suggestion it is evident that the vascular responses described are fundamental to the peripheral regulation of blood pressure.

Summary

Blood-flow changes in human intestine have been detected by means of temperature records from the exposed intestinal tissues of colostomies.

Cold stimulus applied to the body surface produces cutaneous vasoconstriction, intestinal vasodilatation, and a temporary rise in blood pressure.

Removal of cold stimulus from the surface of the body produces cutaneous vasodilatation, intestinal vasoconstriction, and a temporary fall in blood pressure.

Procaine hydrochloride infiltrated into the exposed bowel relaxes vasomotor tone and prevents the occurrence of vasoconstriction in response to heat and of vasodilatation in response to cold, although the vasoconstrictor action of intravenous adrenaline or *nor*adrenaline is not affected.

It is suggested that the intestinal effects are brought about reflexly through the alterations in blood pressure.

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HEXAMETHONIUM BROMIDE IN DUODENAL ULCER

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Paton and Zaimis (1949) have shown that hexamethonium produces blockade of autonomic ganglia. When given intramuscularly it constantly inhibits gastric secretion and motility (Kay and Smith, 1950a). When given by mouth it has a similar though less constant action (Kay and Smith, 1950b). These properties suggest that it may be of value in the treatment of duodenal ulcer.

To evaluate a method of treatment for duodenal ulcer is peculiarly difficult, for it must be based almost entirely on the subjective evidence of the relief of symptoms, and, moreover, there is the danger that improvement due to spontaneous remission may be attributed to the treatment. This paper reports a therapeutic trial designed to avoid these fallacies.

Method of Study

Selection of Cases.—Twenty male patients were taken from those attending the Peptic Ulcer Clinic at the Western Infirmary. Their ages ranged from 21 to 62 years. All had both clinical and radiological evidence of duodenal ulcer and had had symptoms for more than six years. All were suffering severe disability which was refractory to medical treatment and which would ordinarily have merited gastrectomy. Patients known to have pyloric stenosis were excluded, but one patient accepted for trial was later found to have this complication.

Plan of Trial.—Alternate patients were allocated to one of two groups. Group A received hexamethonium bromide (500 mg. at 8 a.m., 2 p.m., and 8 p.m.). Group B received a powder of similar bromide content and similar taste and appearance, consisting of potassium bromide (3 gr.—0.2 g.) made up to bulk with lactose. In all other respects the treatment and assessment of the two groups were identical. The allocation of patients to the two groups and the dispensing of the appropriate powders was done by one of us (L. D. W. S.), who took no part in assessing the results. The assessment was made by A. W. K., who had no means of distinguishing the two groups until the completion of the six-months period of observation. At the outset of this investigation little was known of the side-effects produced by the prolonged oral administration of hexamethonium bromide. It was therefore considered necessary to admit the patients to hospital for six weeks. Thereafter they returned to work and were treated as out-patients for a further 18 weeks. All patients were given ordinary diet from the main kitchen of the hospital unless they complained of severe dyspepsia. Alkali was used only when pain was severe. The patients were encouraged to be up and about during the day and were allowed home on pass one day a week, leaving hospital after lunch and returning at night. After discharge from hospital they were encouraged to take ordinary diet and resume full activities.

Clinical Assessment.—Success or failure in treatment was judged on clinical grounds. The assessment was made on a numerical basis. While in hospital, twice a day each patient was asked by the ward sister if he had any dyspepsia, and the answer was recorded on a chart. If there had been no complaint of any gastric upset a nought ("0") was recorded. Water-brash, heartburn, or discomfort was represented by "1," mild pain by "2," fairly severe pain by "3," and very severe pain by "4." After leaving hospital patients were instructed to keep a similar pain chart. They reported weekly, when further assessment was made by interrogation.

Clinical Results

Group A.—Of the 10 patients treated with hexamethonium bromide six completed the course of 24 weeks. Four were adjudged to be greatly improved, three having remained symptom-free for from 14 to 20 weeks, and the fourth complaining of occasional mild heartburn lasting no more than 10 minutes at a time. Two continued to have mild symptoms. One defaulted after eight weeks though suffering no more than mild dyspepsia at that time. One patient, after seven weeks' treatment without relief, was found to have pyloric stenosis. Two patients suffered severe relapses after periods of improvement and were assessed as failures in the 15th and 23rd weeks.

Group B.—Of the 10 patients treated with potassium bromide, two completed the trial of 24 weeks. None remained symptom-free throughout the period of observation. Two, though continuing to have dyspepsia, were

regarded as somewhat improved. The remainder either gained no relief, or relapsed and were accounted failures, in the 2nd, 4th, 7th, 10th, 11th, 12th, 13th, and 15th weeks.

Side-effects

As hexamethonium bromide given by intramuscular injection is known to cause hypotension in some individuals, particular attention was paid to the cardiovascular system. At first the blood pressure and the pulse rate were recorded twice daily, but in the absence of any noteworthy changes these observations were made only once daily in the later stages of the patients' stay in hospital. A close watch was kept for syncopal attacks, and daily inquiry was made regarding faintness and lightheadedness. Inquiry was also made concerning difficulty in reading as a result of paralysis of accommodation, and a daily note was made of the size of the pupils. The occurrence of constipation, which might conceivably follow the continued use of a ganglionic blocking agent, was also recorded. Since the two groups of patients were indistinguishable, these records were necessarily made in all cases and were not confined to those patients taking hexamethonium bromide.

Group A.—In the group taking hexamethonium bromide the side-effects were with one exception slight or inconstant. The exception was a patient who experienced difficulty in reading while in hospital and who had a minor syncopal attack due to hypotension after dismissal. The dose of the drug was then reduced to 500 mg., taken on retiring, and no further trouble was experienced. This patient developed achlorhydria in response to the drug and was ultimately classed as greatly improved. While in hospital two patients in this group had lightheadedness on standing up and four experienced blurring of vision. These side-effects were noticed only during the first week of treatment or after testing the patient's response to hexamethonium bromide. In this test the patient fasted for a period of seven hours and it seems clear that side-effects are much more likely to occur when the drug is taken in the fasting state. It was further noted that the development of side-effects did not necessarily parallel the change in gastric acidity; hypotension and hypochlorhydria might occur separately. In the continued trial, four patients complained of constipation, which responded to simple measures.

Group B.—Of those patients given potassium bromide, one complained of difficulty in reading for a period of 24 hours and two developed constipation, which they attributed to the treatment.

Effects on Gastric Acidity

Gastric analyses were begun at 9 a.m., after a 12-hour fast. The fasting juice was aspirated, and specimens were removed at half-hour intervals thereafter for three hours. Special precautions were taken to empty the stomach at each aspiration. The volume of each specimen was measured and free and total acids estimated, using the usual double indicator.

Before beginning treatment, two such tests were made on successive days in each case. These analyses were intended to show the gastric acidity in the untreated patient and to serve as a control for future observations.

Subsequently, gastric analysis was made four hours after the administration of a powder. This analysis was intended to serve as a test of each patient's response to hexamethonium bromide, and the interval of four hours was chosen, since it is known that when the drug is effective by mouth a lowered acid level can be expected at this time (Kay and Smith, 1950b).

Once treatment had been started, at weekly intervals an "interval gastric analysis" was made 13 hours after the last dose of powder. These tests were planned to demonstrate any possible cumulative effect resulting from continued administration of the powder.

Results of Gastric Analyses

The results of two preliminary control analyses on each patient confirmed that the level of gastric acidity in any individual may vary from time to time even under standard conditions. Allowance had to be made for this before crediting any observed alteration in acidity to the treatment.

Group A.—In the group of 10 patients taking hexamethonium bromide three developed achlorhydria, as judged by Töpfer's reagent, in response to a test dose. The anacidity persisted during the three hours of the test. Two of these patients were eventually regarded as greatly improved (Fig. 1). One patient, who also became symptom-free, showed a substantial reduction in acid level. An unaffected acid level was found in the remaining six patients; one of these became symptom-free (Fig. 2). In four cases "interval gastric analyses" showed some reduction in the level of gastric acidity, which was maintained throughout the period of observation in hospital (Fig. 3). There was, however, no evidence of progressive diminution of the acid level in response to continued treatment. We

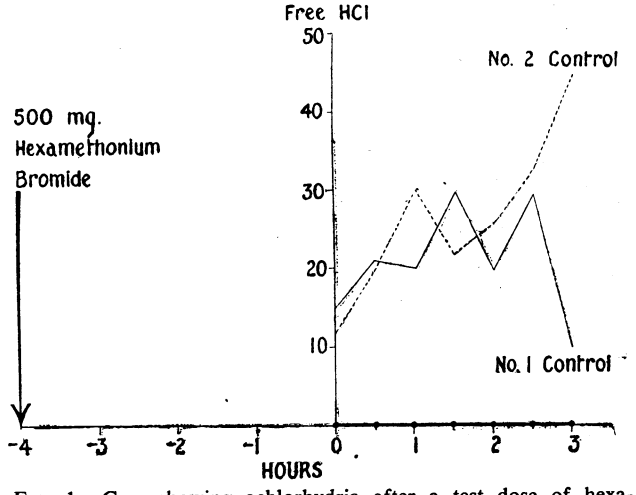

FIG. 1.—Case showing achlorhydria after a test dose of hexamethonium bromide. (The readings for the treated case lie on the base line.) This patient became symptom-free.

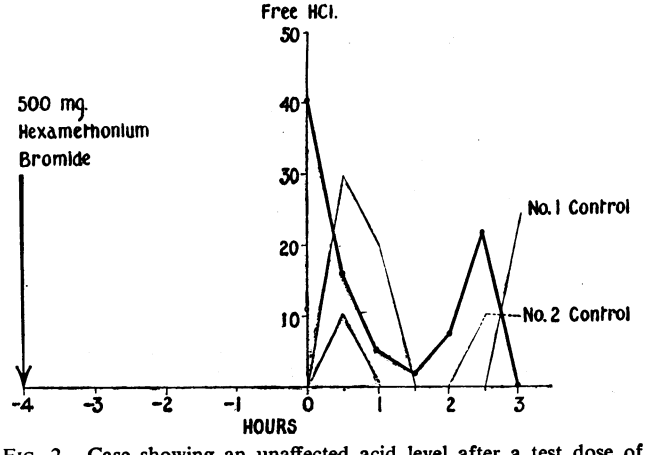

FIG. 2.—Case showing an unaffected acid level after a test dose of hexamethonium bromide. This patient became symptom-free.

have therefore been unable to show that hexamethonium bromide has any cumulative action on the gastric secretion of hydrochloric acid.

Group B.—None of the patients taking potassium bromide showed any change in the acid level that could be attributed to it even on the most optimistic evaluation.

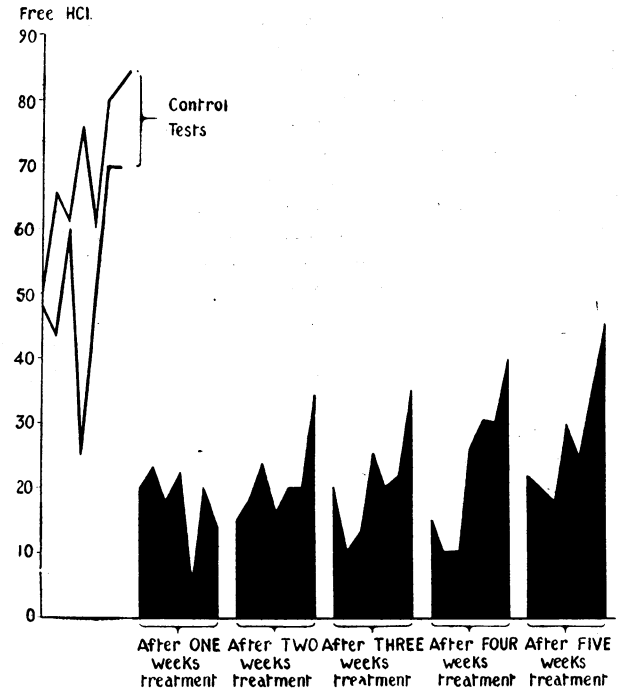

FIG. 3.—Case showing a consistent reduction in acid level as judged by weekly test meals, done 13 hours after the last dose of hexamethonium bromide.

This observation was of importance, since it also showed that the rest in hospital, the freedom from home cares, and the diet taken would not of themselves result in a lowering of gastric acidity.

Discussion

We have already referred to the difficulties in the way of assessing accurately the results of treatment in duodenal ulcer. In particular, there is the fallacy of attributing to the method of treatment under survey improvement due to spontaneous remission. Moreover, in view of the small number of cases in this series and the short period of observation, it is clearly not justifiable to come to any definite conclusion. The results obtained so far do, however, give some evidence of the value of hexamethonium.

It should be noted that all the cases were of the most severe type and completely refractory to orthodox medical treatment. It is therefore not surprising that in Group B (potassium bromide) only two of the ten cases showed partial improvement. On the other hand, in Group A (hexamethonium bromide) the almost complete relief of symptoms in four cases and the partial relief in another two suggest that hexamethonium may be of value in the treatment of duodenal ulcer. If this is so, it remains to be seen how it acts.

We have shown that when taken by mouth the drug can lower the acid level in some cases. However, this action is inconstant and may not be responsible for the clinical improvement. In Group A we observed indisputable lowering of the gastric acidity in four cases. Three of these were ultimately classified as successes and one as a failure. On the other hand, we were unable to show any fall in acidity in one patient who became symptom-free. It is not yet certain that patients showing a marked lowering of gastric acidity at the beginning of treatment will continue to do so after prolonged administration of hexamethonium. Since this drug has a greater effect on gastric acidity in the fasting subject (Kay and Smith, 1950b), its eventual place in the treatment of peptic ulcer may be to control nocturnal hyperacidity. On the other hand, too much attention may have been paid to change in gastric acidity and the action of hexamethonium as an inhibitor of gastric motor activity ignored. Study is continuing on this point.

Useful information has been gained about the side-effects after prolonged administration of hexamethonium. With one exception these effects were slight and the patients were able to continue normal work. Lightheadedness and blurred vision were infrequent, and occurred during the first few days of treatment or when the patient had been fasting. Serious constipation did not occur. The one exception complained of blurred vision and had a minor syncopal attack due to hypotension, but became symptom-free on a single dose of 500 mg. of hexamethonium bromide on retiring. Although the side-effects were infrequent and of a minor nature, we suggest that care should be used, especially in the early days of treatment and when the drug is taken in the fasting state.

Summary

A controlled investigation of the treatment of duodenal ulcer by hexamethonium bromide is reported. While not conclusive, it provides evidence of marked improvement in four and some improvement in two of the ten treated cases. The clinical improvement was not always accompanied by demonstrable reduction in the acidity of the gastric juice. Side-effects occurred most often at the beginning of treatment or when the drug was given to fasting patients.

We are indebted to Professor C. F. W. Illingworth for his direction and helpful criticism throughout this investigation. We wish to acknowledge the assistance given by Dr. A. N. Smith, Dr. Mary Forbes, and Dr. John Raeside. Our thanks are also due to May & Baker Ltd. for generous supplies of hexamethonium bromide.

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An international standard for the adrenocorticotrophic hormone (A.C.T.H.) has been established by the Expert Committee of the World Health Organization on Biological Standardization. The committee also set up international standards for fifteen other biological substances, including anti-Rh, anti-A, and anti-B blood-grouping sera; lecithin and cardiolipin, recently introduced with great success in diagnostic tests for syphilis; tubocurarine, used to obtain muscular relaxation of the patient in anaesthesia; streptomycin and dihydrostreptomycin, the latter being considered to be less toxic than streptomycin and therefore less likely to produce side reactions; aureomycin and terramycin, two new antibiotics which have proved successful where penicillin has previously failed; and diphtheria toxoid, for immunization against diphtheria. A standard was also set up for hyaluronidase (spreading factor), used for intracutaneous injections in small children where intravenous injections would be difficult or impossible. A W.H.O. Expert Committee which had been asked to investigate the possibilities of producing dried smallpox vaccines for the Tropics, where it has been difficult, owing to climatic conditions, to conserve liquid smallpox vaccines in a fresh and active state, recently set up guiding principles to be followed by manufacturers of dried vaccines.