It was relieved in two to four minutes by lying down or walking about, but its presence limits the therapeutic value of these drugs.

It was established that a different response was obtained in upper and lower limbs with the drugs in the doses used in this study. In the lower limbs a rapid and prolonged increase in blood flow and skin temperature occurred after C5 and C6. This approximated closely to that obtained by reflex vasodilatation, and these drugs may therefore be of value in the investigation of peripheral vascular disease in the legs. However, in the upper limbs no significant increases in skin temperature or blood flow occurred in 18 out of 31 tests with C5, and in 16 out of 31 tests with C6; in the remainder the increase in blood flow or skin temperature was slight and in no way comparable to that obtained by reflex vasodilatation. These drugs are therefore unlikely to be useful in the investigation of vasospastic conditions in the upper limb. In the dosage used the vasodilator effect of both C5 and C6 on the lower limb was much greater and more constant than that of T.E.A.B., and the side-effects of C5 and C6 were more pleasant for the patient.

Blood flow to muscle, measured by estimation of forearm blood flow, was not greatly altered.

Sweating was diminished in those digits in which temperature rose.

We wish to record our thanks to Professor Sir James Learmonth and to Mr. D. M. Douglas for much help and advice during the course of the investigation. Our thanks are also due to Dr. W. D. M. Paton, of the National Institute for Medical Research, who visited us twice and discussed the scope of the work with us. We are indebted to Burroughs Wellcome and Co. and to Allen and Hanburys Ltd. for the supplies of the drugs with which these experiments were made.

REFERENCES

- Arnold, P., Goetz, R. H., and Rosenheim, M. L. (1949). *Lancet*, 2, 408.
— and Rosenheim, M. L. (1949). *Ibid.*, 2, 321.
Barcroft, H., and Walker, A. J. (1949). *Ibid.*, 1, 1035.
Organe, G., Paton, W. D. M., and Zaimis, E. J. (1949). *Ibid.*, 1, 21.
Paton, W. D. M., and Zaimis, E. J. (1948a). *Nature*, 161, 718.
— (1948b). *Ibid.*, 162, 810.
Pickering, G. W., and Hess, W. (1933). *Clin. Sci.*, 1, 213.

An account of medical education in Turkey is given in an official publication (*Medico-Social Activity and Organization in Turkey*: Istanbul, 1946) which has just been received in this country. In Istanbul there are residential colleges with accommodation for one thousand students of medicine and related subjects. Board and tuition are given free of charge, and on qualification the graduates are expected to work for the Government for a fixed (but unrevealed) period. Since the establishment of the medical college in 1929 over 1,300 doctors have graduated from it. Turkey previously suffered from a shortage of nurses, as the only organization under which they could receive their training, the Turkish Red Crescent Society, did not produce enough trained women to supply the whole country. The number of nurses' training schools has now been raised to eight, there is a school for midwives in Istanbul, and residential training schools have been set up for village midwives. The report shows that the Turkish Government intends to build health centres in their largest cities. These centres are expected to improve environmental conditions, combat venereal and infectious diseases, and to work for improved infant and maternity hygiene. Apart from their public health activities, the centres will provide facilities for treatment. Each family in the district will have a file of its own, which will be open to Government inspection. The Turkish Ministry of Health has decided that the success of these centres will depend on the quality of their personnel, and has therefore planned that a hundred graduates a year from the School of Hygiene, Ankara, shall be trained for public health work and the best among them sent for further education in the United States. Special training schools will be set up to provide suitable nursing staff. Finally, each health centre is to be equipped with a number of "jeeps" to bring patients in from the outlying countryside.

EFFECT OF HEXAMETHONIUM IODIDE ON GASTRIC SECRETION AND MOTILITY

BY

A. W. KAY, M.D., Ch.M.

AND

A. N. SMITH, M.B., Ch.B.

Hall Tutorial Fellow, University of Glasgow

(From the Peptic Ulcer Clinic, Western Infirmary, Glasgow)

Two principles underlie most of the established methods of treating peptic ulcer—namely, to reduce the acidity of the gastric juice and to relieve spasm. Of the drugs available for these purposes atropine is the most potent, but often it cannot be used owing to its side-effects. Recently tetraethylammonium bromide has been investigated, but its use also is not practicable because of the drug's short-lived action and the unpleasant effects to which it gives rise. In the present paper we report observations on the action of a new compound, hexamethonium iodide (C6), which seems to be more effective and relatively innocuous.

Hexamethonium iodide is a member of the homologous series of polymethylene-bis(trimethyl-ammonium) compounds. Three members of this series have recently been investigated clinically. They all seem to act by impeding the transmission of nerve impulses, but there are striking differences in their point of action and consequently in their effects. Thus the deca-compound (C10) blocks the neuromuscular junction of striated muscle and consequently has a curare-like effect, while the penta-compound (C5) exerts its main action at the preganglionic sympathetic synapses and is effective as a vasodilator.

The hexa-compound (C6), as we shall show, has a profound effect on the gastric secretion and motility, while, at any rate in therapeutic doses, it appears to have no curare-like action and no marked effect on the blood pressure.

Effect of C6 on Gastric Secretion

Ten patients were selected for study, their ages ranging from 22 to 52 years. They were all males with clinical and radiological evidence of duodenal ulcer, and were experiencing severe dyspepsia. While in hospital they were all ambulant save when undergoing investigation. Hexamethonium iodide was the only drug prescribed during their stay in hospital, and they were given the general ward diet.

Secretion tests were begun at 9 a.m. following a 12-hour fast. The fasting juice was aspirated and specimens were removed every fifteen minutes thereafter until the end of the experiment. Special precautions were taken to empty the stomach at each aspiration: alteration in the position of the tube, alteration in the position of the subject (forward and lateral flexion of the trunk), and the application of manual pressure to the abdomen were found to be useful adjuncts towards this end. Using this technique we have been able at all times to secure a specimen of gastric juice when required, even during the studies on spontaneous secretion. All saliva was expectorated during the tests. The volume and bile-staining of each specimen has been noted and the titratable hydrochloric acid estimated in clinical units.

1. *Spontaneous Secretion of Hydrochloric Acid.*—In each subject control observations were made, specimens of gastric juice being aspirated every 15 minutes for a period of three hours. On the following day the same procedure was adopted, but in addition 100 mg. of C6 was given by intramuscular injection immediately after the withdrawal of the fasting juice.

FIG. 1.—Gastric acidity: control readings and after C6.

In each of the 10 subjects there was an immediate fall in the secretion of hydrochloric acid, with a period of complete achlorhydria. In most cases the fall in acidity persisted for about four hours and the anacidity for two to three hours (Fig. 1). The specimens having no free acid were further characterized by low volume and absence of bile.

2. *Gastric Secretion after Insulin.*—Insulin, by inducing hypoglycaemia, has been shown to provoke a pronounced flow of acid secretion in the presence of an intact vagal nerve supply to the stomach (Hollander, 1944). In the control test, 20 units

of soluble insulin was given by intramuscular injection immediately after removal of the fasting juice. On the following day 100 mg. of C6 was given with the insulin injection. The blood sugar in all 10 cases fell below 60 mg. per 100 ml. and all the patients developed symptoms of hypoglycaemia—weakness, hunger, faintness, and sweating. The response to insulin in the control series is shown in Fig. 2, and the effect of C6 on the insulin responses in Fig. 3. The average figures for each series are shown in Fig. 4. In the controls the administration of insulin produced a sharp rise in the level of free hydrochloric acid; when C6 was given with the insulin the level of acidity first fell and then rose to little more than the resting value. Thus C6 prevents the development of a true insulin response.

FIG. 2.—Insulin response in control series.

FIG. 3.—Insulin response after C6.

3. *Gastric Secretion after Histamine.*—In the control test, 0.5 mg. of histamine was given subcutaneously immediately after the withdrawal of the fasting juice, and further specimens were withdrawn and titrated over a period of one and a half hours. On the following day the same dose of histamine was given 45 minutes after the injection of 100 mg. of C6. Typical histamine responses were obtained in five patients with duodenal ulcer, both in the control and in the test observations (Figs. 5 and 6). Thus C6 does not prevent the histamine secretion of hydrochloric acid.

4. *Spontaneous Night Secretion.*—James and Pickering (1949) have produced evidence which supports the belief that duodenal ulcer subjects maintain higher levels of gastric acidity at night than do normal subjects. It is thought that the presence of an abundant and highly acid night secretion may be of importance in the development and maintenance of duodenal ulceration. A study has been made of the action of hexamethonium iodide upon the nocturnal secretion of five patients with active duodenal ulcer. The patients were given neither food nor drink after 5 p.m. A wide-bore stomach-tube with multiple perforations at its tip was passed at 8 p.m. and the stomach emptied. Gastric secretion was then aspirated continuously until 8 a.m., using the constant suction provided by an electric pump. Sedatives were not given. The following evening the experiment was repeated, giving 100 mg. of C6 at 8 p.m., midnight, and 4 a.m. Table I shows that the volume of night secretion was

TABLE I.—Night Secretion Tests

Case No.	Without C6		With C6	
	Volume (ml.)	Free HCl (Clinical Units)	Volume (ml.)	Free HCl (Clinical Units)
1	1,485	70	710	22
2	800	60	330	12
3	730	45	240	12
4	700	15	314	0
5	1,125	60	380	15

FIG. 4.—Insulin response before and after C6—average readings.

reduced by more than half and there was also a marked lowering of acidity. None of the subjects complained of ulcer distress during the night on which C6 was administered, though four had complained of pain during the control test.

Effect of C6 on Gastric Motility

The technique of recording gastric motility has been described by Kay (1947). With the patient fasting for 12 hours, a swallowed balloon is inflated to a standard pressure of 10 ml. of water and connected to a tambour-kymograph unit for recording. The true gastric contraction is represented by a sharp-topped wave of about 30 seconds' duration. A less abrupt regular wave depicts the slow rise and fall of pressure caused by tonic contractions of the fundus. Both of these are superimposed on respiratory oscillations.

Motility records were made in 10 cases of active duodenal ulcer. All cases showed pronounced motor activity with frequent regular contractions. After control periods of observation varying from 20 to 40 minutes, 100 mg. of C6 was given by intramuscular injection. In each case, after a brief latent period, gastric motility was inhibited completely for from $3\frac{1}{2}$ to $4\frac{1}{2}$ hours (Fig. 7). The average duration of inhibition was 3 hours 54 minutes; the longest spontaneous phase of quiescence which can be expected in duodenal ulcer subjects is 30 minutes.

Side-effects

Objective.—Suffusion of the conjunctivae is an almost constant finding and can be discerned within a few minutes

FIG. 5.—Histamine response in control series.

FIG. 6.—Histamine response after C6.

of the injection. The blood pressure and pulse rate were recorded in 12 cases repeatedly for periods of four hours following the intramuscular injection of 100 mg. of hexamethonium iodide. In the supine subject the blood pressure underwent little or no change and there was no increase in pulse rate. On standing there was a slight fall in blood

TABLE II.—Effect of C6 on Blood Pressure
(100 mg. C6 Intramuscularly)

Case No.	Supine		Case No.	Standing for 10 min. periods	
	Resting B.P. (Before C6)	Lowest B.P. Observed after C6		Resting B.P. (Before C6)	Lowest B.P. Observed after C6
1	100/75	95/65	7	100/70	95/65*
2	120/90	110/80	8	110/80	100/70
3	110/80	100/75	9	120/80	110/75
4	110/70	110/70	10	110/70	90/70*
5	110/85	110/85	11	110/80	100/80
6	95/60	95/60	12	115/85	95/65

* Faintness relieved by lying down.

pressure (Table II) and a slight increase in pulse rate. Throughout the investigations the patients were allowed up on several occasions and felt no subjective effects except in two instances.

In these two cases there was a transitory feeling of faintness, quickly relieved on lying down.

Subjective.—There were no untoward subjective effects

in this series. Those patients who at the time of injection had ulcer pain were quickly relieved, and all patients remained free from pain for at least five hours. Hunger sensation was diminished in all cases for three to four hours. This was not accompanied by nausea. Accommodation was slightly impaired in one case in this series. (In more recent cases this side-effect has been more frequent.) Curare-like effects such as ptosis and muscular weakness did not occur. During the period of investigation, which involved several injections of hexamethonium iodide, only one patient complained of constipation. This may have been due to the changes incidental to hospital routine and not to repeated administration of the drug.

Discussion

Our observations show that hexamethonium iodide, when given intramuscularly, inhibits the spontaneous secretion of hydrochloric acid. A single dose of 100 mg. produces achlorhydria for as long as three hours. Repeated doses effect a substantial reduction in the volume and acidity of the night secretion.

The fact that this compound prevents the development of a true insulin response suggests that it acts by vagal blockade. This is in keeping with its known pharmacological action as observed in the experimental animal (Paton and Zaimis, 1949). That it fails to prevent a histamine response is in keeping with the view that histamine acts directly on the parietal cell.

Our observations show also that hexamethonium iodide has a pronounced inhibitory effect on the movements of the stomach. One of us has had the opportunity of testing the effect on gastric motility of many antispasmodic drugs. The four-hour period of inhibition after hexamethonium iodide is greater than has been observed after any other agent. The cessation of gastric contractions and tonus waves is as complete as that resulting from vagal section.

Hexamethonium iodide appears to have several advantages over other drugs with a similar pharmacological action. It is more uniform in its effect, more potent, and of longer duration, and it is relatively free from untoward side-effects.

It seems likely that hexamethonium iodide may have a value in the treatment of peptic ulcer. Certainly it is the most effective drug yet available as an inhibitor of gastric secretion and motility. Up to the present we have employed repeated injections of uniform dosage, and this method is practicable for in-patient treatment. Further observations are in progress on the effects of larger doses, on the use of media for retarding absorption, and on the possibility of oral administration.

Summary

In 10 patients with active duodenal ulcer, hexamethonium iodide inhibited the spontaneous secretion of hydrochloric acid to the point of achlorhydria.

It modified the secretory response to insulin-induced hypoglycaemia but did not affect the response to histamine.

It reduced the volume and acidity of the 12-hour spontaneous night secretion.

It produced prolonged inhibition of gastric motor activity.

The high potency of hexamethonium iodide and

its comparative freedom from undesirable side-effects suggest its use in the treatment of peptic ulcer.

We are indebted to Professor C. F. W. Illingworth for his direction and helpful criticism throughout this investigation and to Dr. F. S. Preston and Dr. J. B. Ritchie for recording observations on blood pressure. Our thanks are also due to May and Baker Ltd. for specially preparing the supplies of hexamethonium iodide.

REFERENCES

- Hollander, F. (1944). *Gastroenterology*, 3, 403.
James, A. H., and Pickering, G. W. (1949). *Clin. Sci.*, 8, 181.
Kay, A. W. (1947). *Lancet*, 1, 448.
Paton, W. D. M., and Zaimis, E. J. (1949). *Brit. J. Pharmacol.*, 4, 381.

CHANGES IN SIZE OF RED CELLS DURING NORMAL PREGNANCY

BY

W. H. H. MERIVALE, M.B., B.S., M.R.C.P.

Pathologist

AND

G. O. RICHARDSON, M.D., M.R.C.P.

Assistant Physician

Departments of Pathology and Medicine, Newcastle-upon-Tyne
General Hospital

Wintrobe and Shumacker (1935) have shown that foetal haemopoiesis is similar to that of patients recovering from pernicious anaemia. Assays of livers of pig foetuses for anti-anaemic potency failed to demonstrate activity save in slight degree in the last third of the gestation period (Wintrobe *et al.*, 1937). If anti-anaemic substance is required for blood formation in the foetus it must be supplied by the mother, so that foetal needs represent an added burden to the pregnant woman. Moreover, Miller and Studdert (1942) noted the common occurrence of defective diets in women suffering from pernicious anaemia of pregnancy. It seems possible that women called on to provide

FIG. 7.—Effect of C6 on gastric motility.