customary. He was the only patient, however, to feel the orthostatic hypotensive effect of hexamethonium, falling flat on his back on rising from bed, four hours after the last dose. All patients were warned not to leave their beds while receiving hexamethonium injections.

Belladonna, or its alkaloid, was given so early in the evening in order that there might be adequate opportunity for absorption of the drug before gastric suction was applied. The residue aspirated after an hour was not tested for unabsorbed belladonna alkaloids. Absorption of belladonna from the small bowel would continue after aspiration had been started. Therapeutically, smaller doses of belladonna should suffice to produce the symptoms of dryness of the mouth and mydriasis on waking, as the drug would be taken at a later hour. In most of the patients studied, data from all of whom are not given in this paper, the administration of belladonna, or its alkaloids, was not continued for any length of time, as it was necessary to withdraw the drug and demonstrate the return of the spontaneous secretion to former levels. However, the drug has been given for periods of many days to other patients to control interdigestive secretion, without ill effect. The use of intramuscular hexamethonium salts is limited to institutional treatment.

Conclusions

Adequate doses—larger than are normally used—of belladonna, or its alkaloids, orally, and intramuscular hexamethonium iodide produce substantial inhibition of interdigestive gastric secretion in patients with duodenal ulcer. The inhibition obtained compares favourably with a series studied by Clarke *et al.* (1947) before and after the operation of vagotomy. In 16 patients they found a reduction by a half of the average total acid output.

Summary

The effects of oral belladonna, or L-hyoscyamine, and hexamethonium iodide intramuscularly on interdigestive gastric secretion are compared.

Similar substantial reduction in secretion volume and acid and pepsin output is obtained by means of either drug. Results compare favourably with a reported series after vagotomy.

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REFERENCES

Avey, H. T., Musick, V. H., Hopps, H. C., and Hellbaum, A. A. (1950). *Gastroenterology*, **14**, 386.
Clarke, J. S., Storer, E. H., and Dragstedt, L. R. (1947). *J. clin. Invest.*, **26**, 784.
Dragstedt, L. R. (1942). *Arch. Surg., Chicago*, **44**, 438.
—— and Owens, F. M. (1943). *Proc. Soc. exp. Biol., N.Y.*, **53**, 152.
Ferrer, J. M. (1948). *Surg. Gynec. Obstet.*, **87**, 76.
Goodman, L., and Gilman, A. (1941). *The Pharmacological Basis of Therapeutics*, p. 462. Macmillan, New York.
Henning, N., and Norpoth, L. (1933). *Arch. VerdauKr.*, **53**, 64.
Hunt, J. N. (1948). *Biochem. J.*, **42**, 104.
James, A. H., and Pickering, G. W. (1949). *Clin. Sci.*, **8**, 181.
Kay, A. W., and Smith, A. N. (1950a). *British Medical Journal*, **1**, 460.
—— —— (1950b). Ibid., **2**, 807.
Keefer, C. S., and Bloomfield, A. L. (1926). *Arch. intern. Med.*, **38**, 303.
Kirsner, J. B., Levin, E., and Palmer, W. L. (1948). *Gastroenterology*, **11**, 598.
Levin, E., Kirsner, J. B., and Palmer, W. L. (1949). *J. Lab. clin. Med.*, **34**, 1620.
Lorber, S. H. (1950). In H. C. Bockus's *Postgraduate Gastroenterology*. Philadelphia.
Mears, F. B. (1943). *Surgery*, **13**, 214.
Smith, C. A., Woodward, E. R., Janes, C. W., and Dragstedt, L. R. (1950). *Gastroenterology*, **15**, 718.

MECHANISM OF THE RENAL EXCRETION OF METHONIUM COMPOUNDS

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It has been reported (Milne and Oleesky, 1951) that in normal man hexamethonium bromide given intramuscularly is almost completely excreted in the urine in the 24 hours following the injection. Zaimis (1950) has also shown that in rabbits 60 to 70% of an intravenous dose of hexamethonium iodide is excreted in the urine during the next 24 to 48 hours. The following observations were made to find out in what manner the kidneys excrete hexamethonium bromide (C6) and pentamethonium bromide (C5). The clearance of these substances has been compared with the simultaneous clearance of inulin in man and experimental animals.

Technique

Clearances were estimated in two unanaesthetized hypertensive patients and in three subjects during varicose-vein ligation or herniorrhaphy under light ether or cyclopropane anaesthesia ; in three cats ; and in four rabbits anaesthetized with pentobarbitone sodium 40 to 60 mg./kg., or chloralose 75 mg./kg.

Inulin clearance was taken to equal glomerular filtration rate. An intravenous priming injection of inulin was given, followed by an intravenous maintenance injection delivered by an electrically driven syringe. At least half an hour was allowed for stabilization before clearance periods were begun.

The administration of C5 and C6 was not uniform. The two hypertensive patients had been on methonium compounds for several weeks before the day of the experiments, and a plasma and urine blank was therefore not obtainable. In these two patients 50 mg. of methonium compound was given intramuscularly 15 minutes before the start of the first clearance period, followed by an intravenous maintenance of 0.5–1 mg. a minute. In the three anaesthetized subjects C5 was given intravenously in divided doses, and clearance periods were begun 5 to 10 minutes after the last injection ; no C5 was given during the clearance periods. The cats and rabbits were given an intravenous priming injection of C6, 1 to 3 mg./kg., in divided doses, 5 to 20 minutes before the start of the first clearance period. Only three animals were given a C6 intravenous maintenance injection (16 μg. a minute) during the clearance periods.

A diuresis was promoted by a continuous intravenous injection of 8 to 12% mannitol in the anaesthetized subjects and experimental animals. In the two unanaesthetized subjects a brisk diuresis was induced by 1,000 ml. of water given by mouth an hour before the first clearance period. Urine was collected by urinary catheter in all instances, the bladder being washed out with saline at

the end of each clearance period. The duration of clearance periods was 10 to 15 minutes.

Heparinized venous blood was collected near the mid-point of each period for estimation of plasma inulin and C5 or C6. Protein precipitation was with cadmium sulphate (Goldring and Chasis, 1944), and inulin was estimated by the method of Roe *et al.* (1949). The plasma and urine methonium levels were estimated on the nictitating membrane preparation, in the cat, by close arterial injection into the superior cervical ganglion. The peripheral end of the cut cervical sympathetic nerve was stimulated continuously to give a constant and maximum retraction of the membrane; untreated plasma and diluted urine were delivered to the superior cervical ganglion by a retrograde injection into the external carotid, which was ligated peripherally. The ganglionic block produced by methonium activity decreased the retraction of the nictitating membrane, and the extent of this relaxation was calibrated by injection of standard concentrations of methonium compounds. A description of this biological assay will be published shortly by Dr. W. D. M. Paton, who was very generous in teaching us the technique.

Results and Comments

The results are shown in the Table. The clearance figures are the average of two or three periods.

The Simultaneous Renal Clearances of Hexamethonium or Pentamethonium Bromide and Inulin

	Anaesthetic	Methonium Compound	Plasma Level C5 or C6 (μg./ml.)	Renal Clearance (ml./min.)		C5 or C6 / Inulin Clearance Ratio
				C5 or C6	Inulin	
Subjects						
1 ..	None	C5	7·2	51	57	0·9
2 ..	,,	C6	5·3	97	94	1·0
3 ..	Ether	C5	5·1	121	97	1·2
4 ..	,,	C5	3·6	154	110	1·4
5 ..	Cyclopropane	C5	5·1	62	61	1·0
Average						1·1
Cats						
1 ..	Pentobarbitone sodium	C6	2·0	7·8	6·8	1·1
2 ..	,,	C6	3·6	10·8	10·0	1·1
3 ..	Chloralose	C6	4·6	5·7	4·7	1·2
Average						1·1
Rabbits						
1 ..	Pentobarbitone sodium	C6	3·0	3·2	4·5	0·7
2 ..	,,	C6	12·5	7·4	5·3	1·6
3 ..	,,	C6	5·9	6·3	6·4	1·0
4 ..	,,	C6	6·4	5·0	3·4	1·4
Average						1·2

The average methonium : inulin clearance ratio is 1.1 in man and the cat and 1.2 in the rabbit. It is clear from these ratios that the renal excretion of C5 and C6 is mainly due to filtration, with some minimal excretion by the tubules. It follows, therefore, that the maintenance dosage of these methonium compounds should be proportionately less in cases in which the glomerular filtration rate is reduced.

Summary

The mechanism of the renal excretion of hexamethonium and pentamethonium bromide has been studied in man, the cat, and the rabbit by comparing their clearances with the simultaneous clearance of inulin.

The methonium : inulin clearance ratios were 1.1 to 1.2, indicating that the renal excretion of these methonium compounds is mainly due to glomerular filtration, with minimal tubular excretion.

REFERENCES

Goldring, W., and Chasis, H. (1944). *Hypertension and Hypertensive Disease.* New York.
Milne, G. E., and Oleesky, S. (1951). *Lancet*, **1**, 889.
Roe, J. H., Epstein, J. H., and Goldstein, N. P. (1949). *J. biol. Chem.*, **178**, 839.
Zaimis, E. J. (1950). *Brit. J. Pharmacol.*, **5**, 424.

Medical Memoranda

Streptomycin and Friedländer's Bacillus

This case is of interest because it shows how a bacteriological investigation may be of value in guiding the choice of treatment.

Case Report

The patient, a middle-aged woman in good general health, had suffered from recurrent attacks of sinusitis in both left and right maxillary antra since 1937, when a left intranasal antrostomy and turbinectomy was performed. This operation was undertaken on the strength of a radiological abnormality found during a search for septic foci to account for a rheumatic episode.

The long-term result of the operation was not wholly successful and a variable amount of discharge had come from the sinuses ever since, with, from time to time, acute attacks of pain, headache, and sometimes fever. These had become more frequent recently, as many as a dozen having occurred during the past two years. The patient habitually treated such attacks with nose drops of a sulphonamide compound, and the acute condition usually cleared up in a few days.

In March, 1950, she developed one of her usual "acute" attacks of sinusitis on the left side. The attack failed to respond to sulphonamide drops, pain and headache remained, and the discharge from the nose became thick and yellow.

On April 17 a left nasal swab was submitted for bacteriological examination and a profuse pure growth of a Friedländer's bacillus was obtained. The organism was non-motile and capsulated, and had the following biochemical reactions after 24 hours' growth at 37° C.: Lactose − ; glucose A.G.; mannitol A.G.; sucrose − ; salicin A.G.; dulcitol − ; maltose A.G.; indole +.

Plate-sensitivity tests were performed, with the following results. Resistant: penicillin, sulphanilamide, sulphacetamide, methyl violet; slightly sensitive: sulphadiazine, phenoxetol; very sensitive: streptomycin.

On May 3 this organism was still present, and so were the symptoms. Meanwhile the patient had been using inhalants and decongestive drugs and twice-weekly short-wave diathermy had been started, all without effect. Indeed, a brief exacerbation of headache had following each diathermy session.

Treatment by direct attack against the Friedländer's bacillus was then considered. "Aureomycin" and chloramphenicol were not available at the time. Streptomycin was the available drug to which the organism was most sensitive, but it had the disadvantages of being likely to produce rapid development of bacterial resistance if used locally and of involving daily intramuscular injections and possibly toxic side-effects if used systemically. Accordingly it was decided to try first of all the effect of local treatment with phenoxetol, to which the organism showed some sensitivity.

A 2% solution of phenoxetol in physiological saline was used, a few drops being instilled into the nose four times daily. Unfortunately this solution caused smarting pain