

GANGLION BLOCKING AGENTS

Roy D. H. Maxwell,
Royal Alexandra Infirmary, Paisley.

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Research into the production of synthetic curarising agents led in 1948 to the discovery of the marked activity of the fifth and sixth members of the polymethylene-bistrimethylammonium series of compounds in blocking autonomic nervous ganglia. These drugs were applied therapeutically to lower the blood pressure of patients suffering from hypertension and to control the gastric secretion in peptic ulceration. In view of the limitations to which they are subject in these applications, in 1950 I initiated a programme of research directed mainly to the production and examination of homologues of this series of compounds. Other synthetic compounds of potential usefulness were included in this examination.

Clinical experience was obtained with the synthetic ganglion blocking agent hexamethonium, and with atropine and methantheline which are in current use in the control of hypertension and gastric secretion. Certain of the new compounds were selected for comparison with these drugs, several new compounds requiring examination because of the limited value of the biological techniques available.

From the clinical investigation two new compounds were selected which have a useful degree of activity in blocking autonomic ganglion transmission. The first of these, pentapyrrolidinium, is highly active and fairly selective in

inhibiting sympathetic ganglia, and the second ethyltetramethonium, although less active, has a preponderance of activity at the vagal ganglia. The former drug is now in use for the treatment of hypertension, and the latter will probably be used in the treatment of duodenal ulceration.

The considerations applied in the design of the new compounds are reviewed, the results of biological assessment are given, together with methods used and results obtained during the initial examination of their effects in man.

The possibilities of the control of hypertension and peptic ulceration by drugs are described and the results obtained with the new drugs are recorded. Possible future methods of therapy of these conditions are discussed. A bibliography is appended containing a list of the references read in the preparation of this study. A number of publications have been based upon this work of which those I have written jointly or otherwise are as follows:-

1. Treatment of hypertension with oral methonium compounds. 1952 - British Medical Journal.
2. New sympathicolytic agents. 1953 - Lancet.
3. Diseases of the cardiovascular system. 1954 - Annual Review of Medicine, Vol. 5, 51, Annual Review Inc., Stanford, California, U.S.A.
4. Ethyltetramethonium in control of gastric secretion. Awaiting publication.
5. The medical treatment of hypertension. 1954 - British Medical Journal - In press.

6. Treatment of malignant hypertension.
Awaiting publication.

Reprints of the first three articles are submitted, together with typescripts of the fourth and fifth. The material of the sixth is contained in the text.

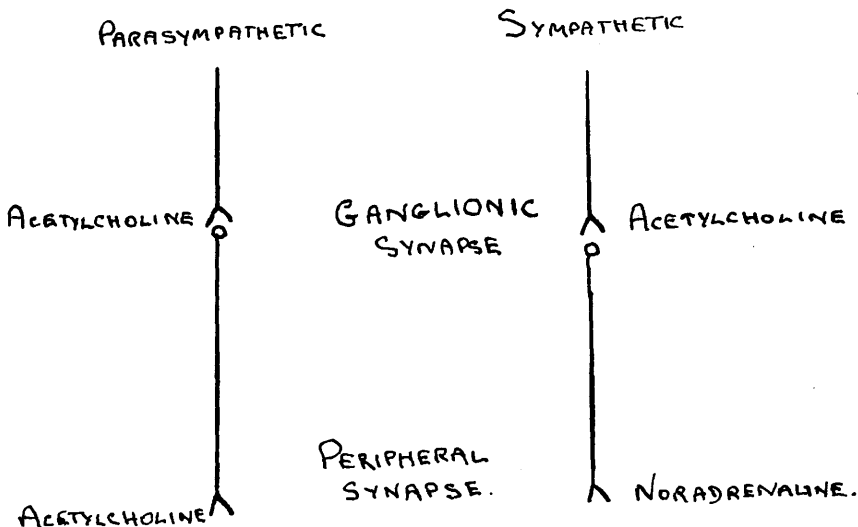
SECTION I

In this section the experimental work leading to, and the indications for, the development of new compounds affecting autonomic nervous activity are reviewed. The considerations involved in the preparation and selection of new compounds are given, together with abbreviated biological findings. The methods of investigation of the new compounds selected for examination in man are noted, and the results obtained are summarised. The possibilities for future work are discussed.

CHEMICAL TRANSMISSION

The conducting pathways of the nervous system involve a cell with a nerve fibre which terminates in close relationship to the next cell or to the receptor site, the intervening gap being termed a synapse. The conduction of nerve impulses involves therefore, not only an action potential in the axone, but also a chemical transmission across the synapse. In 1914, Dale demonstrated that certain esters and ethers of choline reproduce the effect of autonomic and motor nerve stimulation, and subsequently identified acetylcholine as the most active at the autonomic ganglia, parasympathetic postganglionic terminations, and motor nerve terminations. Von Euler in 1946 recognised the activity of adrenaline and noradrenaline at the sympathetic postganglionic terminations.

These sites of activity may be shown diagrammatically as follows:-



INHIBITION OF CHEMICAL TRANSMISSION

While the discovery of the chemical transmitters involved in autonomic nervous function enabled stimulation by the use of the sympathins and by acetylcholine or more stable parasympathomimetics, it has been difficult to secure a pure inhibition of activity by drug action. In the case of the parasympathetic component of the autonomic nervous system, atropine paralyses postganglionic transmissions without inhibiting acetylcholine liberation by acting upon the receptor site. However the action of this alkaloid is complex as it is a central nervous stimulant and produces also some inhibition of ganglionic conduction. The autonomic ganglia may be paralysed by nicotine, but the action of this alkaloid is complex also as the paralysis it produces is preceded by stimulation, and it affects also the central nervous system and motor nerve endings.

Paralysis of the neuromuscular transmission has been more readily obtained by alkaloids of curare. It was by study of these that the new synthetic drugs affecting autonomic transmission have been obtained.

CURARISING AGENTS

Curare

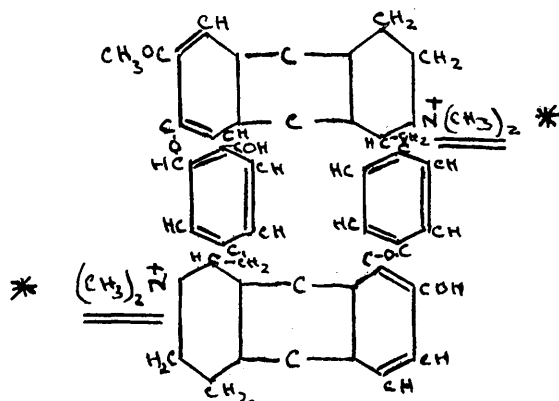
The site of action was identified first by Langley (1909),

who advanced the hypothesis that curare prevented the action of nerve stimuli by combining with receptive substances at the myoneural junction. Confirmatory evidence of this suggestion was given by the experiments by Brown and Feldberg (1936) who demonstrated that during superior cervical sympathetic ganglionic paralysis by curare, preganglionic nerve stimulation still resulted in acetylcholine liberation; and Dale et al (1936) found normal acetylcholine release following hypoglossal nerve stimulation in the perfused cat's tongue. Studies of motor end plate potentials by Eccles et al (1941) and others, have shown that curare opposes the depolarising action of acetylcholine, and it has been suggested that the quaternary ammonium groups of curare compete with the quaternary ammonium termination of acetylcholine for fixation at the receptors.

In man, the muscle paralysing dose of curare produces no systemic toxicity and it is possible to induce complete muscular paralysis in a dose which does not affect other functions. The value of such a drug in modern anaesthesia was appreciated by Griffith and Johnson (1942). The composition of natural curare is indefinite and variable, and the sources of supply were initially unreliable as has been described by McIntyre (1947). D-tubocurarine was isolated from tubocurare by King (1935). The Wellcome Foundation was responsible for the preparation of pure alkaloid standardised by the rabbit

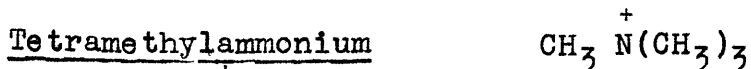
head drop (Bennett, 1950), rat phrenic nerve-diaphragm preparation (Bulbring, 1946), or mouse method (Skinner and Young, 1947). The effect in man of the pure alkaloid was studied by Prescott et al (1946), of the Medical Advisory Staff of Burroughs Wellcome Ltd.

During this research, attempts were being made to produce synthetic curarising agents which would overcome supply difficulties and provide readily chemically pure drugs of constant action. Craig (1948) has reviewed the relationship of chemical structure to curarising action. The structural formula of d-tubocurarine is as follows:-



D-tubocurarine - * the presence of two quaternary ammonium groups is to be noted.

MONOQUATERNARY AMINES



Burn and Dale (1914) examined the pharmacological actions of tetramethylammonium. It was found to produce peripheral muscarine-like inhibition of heart rate and output; and a

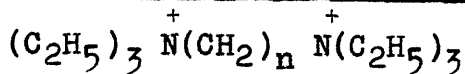
nicotine-like stimulation of sympathetic ganglion cells with an initial rise in blood pressure, followed by paralysis of ganglion cells with a fall in blood pressure. It is a weak curarising agent.

Tetraethylammonium $C_2H_5 \overset{+}{N}(C_2H_5)_3$

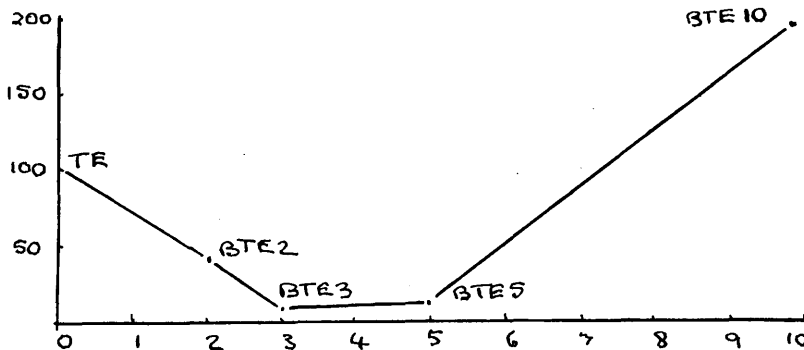
Tetraethylammonium is relatively devoid of curarising activity. It produces paralysis of ganglion cells with a preliminary phase of stimulation. Acheson and Moe (1946) investigated this effect further, demonstrating that tetraethylammonium produces a fairly selective ganglion block. Unfortunately the actions of tetraethylammonium in man are complex. They have been studied by Lyons et al (1947), Birchall et al (1947), and Boyd et al (1948). Although a good depression in the blood pressure with postural hypotension followed intramuscular injection of 1-2 g., unpleasant side effects occurred, such as a metallic taste, and sensations in the hands and feet of numbness cold and tingling. Inhibition of gastric peristalsis was demonstrated by Holt et al (1947) and McDonald and Smith (1949) showed inhibition of spontaneous gastric secretion. Despite its unpleasant side effects, tetraethylammonium has been used by Berry et al (1946), Lyons et al (1947) and many others in an attempt to reduce the blood pressure of patients with essential hypertension.

THE BISQUATERNARY AMINES

The Polymethylene bistriethylammonium Series



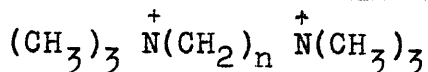
Much of our knowledge of the pharmacological actions of onium compounds is due to the studies by Ing. In 1936 he advanced the hypothesis that the extraordinary potency of tubocurarine in blocking neuromuscular transmission in comparison with that of simple quaternary ammonium salts might be due in part to the presence of two such cationic groups at some optimal distance apart. Chou and DeEllo (1947) examined the effect of four drugs of the general formula, n 2 prepared by Ing, n 3, 5 and 10 prepared by Barlow, using cat superior cervical ganglion preparation of Kibjakow (1933) as modified by Feldberg and Gaddum (1934). The relationship they found of the activity of these compounds to the number of carbon atoms in the polymethylene chain in comparison with tetraethylammonium was as follows:-



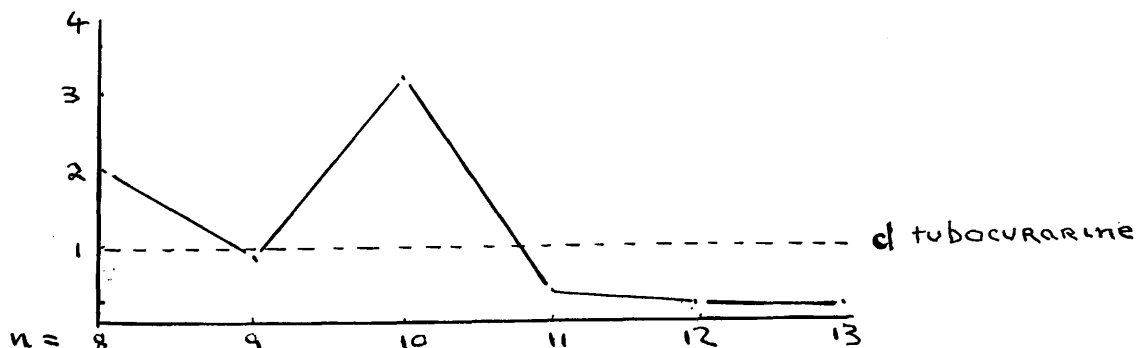
The relationship between the activity of tetraethylammonium bromide (TE), given a value of 100, and of bistriethylammonium bromides (BTE2, BTE3, BTE5, and BTE10) in the perfused sympathetic ganglion of the cat. Ordinate: percentage potency. Abscissae: Number of carbon atoms in the polymethylene chain of the molecule.

It is to be noted that the bistriethylammonium C.10 was twice as potent as tetraethylammonium.

The Polymethylene bistrimethylammonium Series



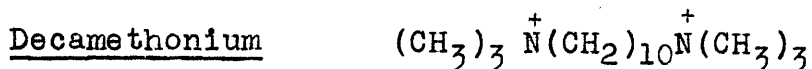
Barlow and Ing (1948) themselves extended the examination of the polymethylene bisquaternary ammonium salts, comparing the methyl homologues with the ethyl. They confirmed the study of Chou and DeElio using the phrenic nerve-diaphragm preparation of the rat, showing an increase in curarising activity in the triethylammonium series from C.4 - C.13, and they found in the trimethylammonium series a progressive rise from 7th - 9th member, the activity remained fairly constant to the 12th, with a fall at the 13th. Using the rabbit head drop test, it was found that the C.10 in the trimethyl series was about three times as potent as tubocurarine. The activity in comparison with tubocurarine was as follows:-



Simultaneously, Paton and Zaimis (1948) reported identical results. They had been concerned with the study of compounds

producing liberation of histamine, and during examination of the C.8 of the bistrimethyl series, they had observed remarkable neuromuscular blocking activity. Proceeding further using the rabbit head drop test, they confirmed the high activity of C.10 (decamethonium).

SYNTHETIC CURARISING AGENTS

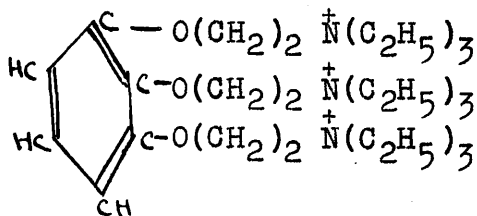


The systematic study of Ing, and the chance finding of Paton, resulted in the discovery that this simple synthetic compound will reproduce the neuromuscular paralysis occasioned by the complex alkaloid tubocurarine in animals. The effect in man was examined by Organe et al (1949) who found that 3 mg. of decamethonium iodide intravenously produced a degree of paralysis in the conscious subject comparable with 15-20 mg. of d-tubocurarine chloride. In common with tubocurarine, in high dosage decamethonium produced some depression of sympathetic ganglion transmission, 20-40 mg. intravenously being followed by cutaneous vasodilation and postural hypotension.

Gallamine (Flaxedil) - R.P. 3697

Studying simplifications of the tubocurarine molecule for the French chemical manufacturers, Rhone Poulenc Freres, Bovet et al (1947-49) prepared a number of compounds of which compound 3697 R.P. was found to be a powerful curarising agent with a very weak ganglion blocking action. Its formula is

as follows:-



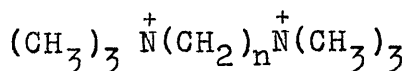
1 : 2 : 3 - Tri(B-dimethylaminoethoxy) benzene

Wien (1948) has recorded its pharmacological actions in the animal, and Mushin et al (1949) first used this drug in anaesthesia.

Synthetic Ganglion Blocking Agents

The high degree of curarising activity of decamethonium led to examination of the pharmacological properties of other members of this series of compounds, with the discovery of the marked ganglion blocking properties of shorter chain members. Paton and Zaimis (1948) drew attention to the ganglion blocking activity as well as the neuromuscular block which could be produced by these compounds, and in 1949 they prepared a comprehensive study of their pharmacological actions.

The basic formula of the alkamethonium compounds is as follows:-



the members of this homologous series being designated by the number of carbon atoms (n) in the polymethylene chain. The second to the thirteenth member inclusive, and the eighteenth member have been examined by Paton and Zaimis (1949), and the effect of these compounds upon autonomic ganglionic transmission was as follows:-

Relative potencies in causing relaxation of cat's nictitating membrane, exciting by stimulation of cervical sympathetic trunk

(Arbitrary scale, C.6 100)

Compound:	C4	C5	C6	C7	C8	tetraethyl- ammonium iodide
Potency:	2	80	100	10	2	5

Relative potencies on peristaltic reflex of small intestine

Compound:	C2	C3	C4	C5	C6	C7	tetraethyl- ammonium iodide
Potency:	3.0	4.3	5.9	33.3	100	16.7	14

The marked activity of the penta and hexa compounds in inhibiting sympathetic stimulation and peristalsis is to be noted, the chain length is critical.

HEXAMETHONIUM

In contrast with tetraethylammonium and certain alkaloids, hexamethonium produces paralysis of autonomic ganglia without initial excitation, the action is slower in onset than that of tetraethylammonium and is three to four times more prolonged; and hexamethonium is much more active. The site of action is upon the receptive site, no interference occurring with histamine release at the synapse as has been shown by Paton and Zaimis (1951) and Feldberg (1951).

The actions of hexamethonium in the animal are due to selective autonomic ganglion blockade and are as follows:-

a) Due to action on sympathetic ganglia

- i. Inhibition of response to preganglionic stimulation of the cervical ganglion (cat).
- ii. Increased peripheral blood flow in the ear (rabbit).
- iii. Hypotensive action.
- iv. Increased gastric motility in the cat. (Wien and Mason 1951).
- v. Increased sensitivity of dogs to insulin. (Schachter 1951)

b) Due to action on parasympathetic ganglia

- i. Inhibition of the peristaltic reflex in the ileum (rabbit).
- ii. Inhibition of bradycardia and hypotension resulting from vagal stimulation.
- iii. Mydriasis due to ciliary ganglion paralysis.
- iv. Reduction in the volume and acidity of gastric secretion in dogs in response to vagal stimulation (Wien and Mason 1951, Flowe et al 1951).

Hexamethonium will be of great importance in future experimental studies upon the function of autonomic nervous system. The almost entirely selective paralysis of autonomic ganglia which it occasions in the absence of any preliminary excitation offers possibilities of more accurate studies than

obtainable previously with alkaloids of complex action.

ACTIONS OF HEXAMETHONIUM IN MAN

Some of the early investigations of the actions of the methonium compounds in man were performed with pentamethonium. It was found that this member of the series was rather less active than hexamethonium, and subsequent studies were upon the latter drug. Organe, Paton and Zaimis quickly appreciated the possibility of applying pentamethonium in the treatment of hypertension as a better drug than tetraethylammonium; in 1949 they determined the effect upon the blood pressure in man with pentamethonium. Their investigation was followed by those of Arnold and Rosenheim (1949), Arnold et al (1949), Grob et al (1949), Restall and Smirk (1950), and Smirk (1950). The results of these experiments showed that the intravenous injection of 25-100 mg. of pentamethonium iodide produced a fall in the systolic and diastolic blood pressure of normal and hypertensive patients of a duration of up to several hours. That the fall was due to a decrease in peripheral resistance following relaxation of sympathetic tonus was demonstrated by the Goetz' optical digital plethysmograph.

Subsequent investigation of possible usefulness in therapeutics followed rapidly.

Hypertension

Saville (1950), Turner (1950), Campbell and Robertson (1950), and Grob and Harvey (1950), were the first to report

upon the results which were obtained by lowering the blood pressure in patients with hypertension suffering from severe symptoms and signs. It was agreed that an improvement followed reduction in the blood pressure comparable with that following sympathectomy, and this was endorsed particularly by Mackey and Shaw (1951), one of these authors having had extensive experience of operative procedures.

Controlled Hypertension During Anaesthesia.

The gravitation of the blood to dependent limbs with relaxed arteriolar tonus was appreciated by Enderby (1950) as a method of obtaining an area of surgical operation unobscured by haemorrhage. This work was extended by Davison (1950), and the methods were commented upon further by Enderby (1951), Enderby and Belmore (1951), Lewis (1951), D'Audigne and Kern (1951), Scurr (1951), Shackleton (1951), and others.

Peripheral Vascular Disease

The increase in peripheral circulation which followed dosage of methonium compounds was used in the treatment of peripheral vascular disease by Burt and Graham (1950), followed by Finnerty and Freis (1951). This work was limited as an increase in peripheral circulation was attended by hypotension.

Peptic Ulceration

Following upon the earlier studies with tetraethylammonium, Kay and Smith (1950a & b) demonstrated suppression of gastric secretion and motility. Douthwaite and Thorne (1951) showed

that this effect could be obtained only in the presence of hypotension. In extension of their studies, Kay and Smith (1951) correlated the activity of C.4, 5, 6 and 7, suppressing gastric secretion with the activity curve in paralysing the superior cervical ganglion in the cat prepared by Paton and Zaimis (1949). The potential importance of this drug in the treatment of duodenal ulceration was examined by Scott et al (1950) which showed that oral dosage of hexamethonium was of some value in the treatment of severe duodenal ulceration, and their work has been confirmed by Bartels (1952).

The application of hexamethonium in the therapy of peptic ulceration was limited by its activity in producing hypotension, by uncertainty of action when administered orally, and by a rapid acquisition of tolerance necessitating high dosage.

Hyperhidrosis

The depression of vagal tone responsible for excessive sweat secretion produced by hexamethonium was commented upon by Chalmers and Keele (1952), and Sommerville and McMillan (1952) have used hexamethonium in the treatment of hyperhidrosis.

Limitations to Methonium Therapy

Dosage of hexamethonium in man produces the following results:-

1. A fall in the diastolic and systolic blood pressures. With Campbell (1953) I demonstrated in the normotensive subject in the recumbent posture with sufficient dosage, i.e. 50 mg. hexamethonium cation subcutaneously, the diastolic blood pressure falls to 40 - 60 mm., the systolic pressure being some 30 mm. higher. This level probably represents maximum vasodilation following complete inhibition of sympathetic vasomotor tonus. The fall in blood pressure is more spectacular in hypertensive patients as the initial level of blood pressure is higher, the basal diastolic pressure reached varied from 60 - 100 mm., and is probably an indication of the elasticity of the vessels and intravascular fluid volume. Assumption of erect posture under these conditions was followed by an immediate loss of consciousness which is liable to be accompanied by trauma if precautions are not taken to prevent the patient falling. The lack of premonitory symptoms of inadequate cerebral blood pressure constitutes a grave risk which has limited the dosage and the reduction of the blood pressure of ambulant patients, and this risk is increased by variations in individual sensitivity to the drug, and variations in absorption when it is administered by the oral route.

2. In a proportion of patients inhibition of vagal tonus is followed by diminished peristalsis, affecting the intestine as well as the stomach, with the production of constipation which

if untreated will be followed by ileus. Mackey and Shaw (1951) and others have reported upon paralytic ileus during hexamethonium treatment. This complication followed oral dosage more often than systemic dosage and has necessitated on some occasions withdrawal of treatment. The intestinal stasis and hyperaemia sometimes results in diarrhoea which is also a contraindication to further dosage.

3. The other side-effects of methonium therapy in the form of mydriasis, dryness of the mouth and inhibition of sweat secretion, have not limited the usefulness of this drug.

From a therapeutic viewpoint, the limitations of hexamethonium are therefore its inability to lower the blood pressure without inhibiting gastrointestinal activity, and conversely, it cannot be applied to decrease gastric secretomotor activity without the risk of producing hypotension. The first function is due to inhibition of the sympathetic component of the autonomic nervous system and the second the parasympathetic. Further limitations which have been encountered during clinical studies and which have been commented upon by myself with Graham and Campbell (1952), and others, have been inconsistency of action due to individual variation and sensitivity, rapid acquisition of tolerance necessitating progressive increase in dosage to high levels, Locket et al (1951) having used up to 12 gm. per day orally; and wide fluctuations in the blood pressure during treatment of hypertensive patients, possibly due to inhibition of the

parasympathetic as well as the sympathetic autonomic ganglia.

However, hexamethonium has been the most effective drug so far discovered in lowering the blood pressure, and inhibiting gastric secretomotor activity. The developments of further ganglion blocking agents appears to be desirable therefore, with the object of obtaining new compounds which would be at least in part an improvement compared to hexamethonium, and other drugs having some of the actions of hexamethonium, i.e. ganglion blocking agents having a predominance of action on the sympathetic ganglia, or parasympathetic ganglia, affecting mainly one or the other.

CHEMISTRY

In February 1950, I prepared a preliminary report detailing the necessity for research upon compounds which would be of use in the treatment of hypertension and peptic ulceration. The main possibilities at that time were the development of ganglion blocking agents based upon hexamethonium of selective action; and the examination of a number of monoquaternary amines.

Methonium Homologues

Slight differences between hexamethonium and pentamethonium are apparent in the pharmacological and clinical studies, e.g. tachycardia was pronounced with pentamethonium and less marked during the action of hexamethonium. Further modification of this series appeared to be indicated, and in particular study of the partial ethyl homologues was desirable in view of the differences in action between the bistriethyl and bistrimethyl series and tetraethylammonium and tetramethylammonium. Further, substitution of the chain and terminations by other chemical structures was indicated to determine the essential parts of the molecule. It was anticipated that the bisquaternary amines would be ganglion blocking agents, and these might have a useful preponderance of activity.

Monoquaternary Amines

The gastric antisecretory drugs described in the literature of monoquaternary type such as Banthine and Dibutoline, active at the peripheral vagal synapse, have atropine-like side actions limiting their usefulness. The inclusion in this study of a

number of other monoquaternary amines was considered advisable in the hope of finding one with a more selective action upon gastric secretomotor activity.

In April 1950, with the permission of Professor Paul of Rhone Poulenc Freres in Paris, I surveyed the pharmacological data obtained upon a number of new compounds prepared by Bovet and Decourt. These had been examined for antihistamine and curarising activity mainly, but their anticholinergic properties had been determined. With the advice of Professor Paul, a few of these were selected for clinical examination, the quantities required being prepared by May and Baker Ltd.

NEW COMPOUNDS

Within the programme of work I prepared, a number of groups of new compounds were made, each being prepared as a series because of the necessity to determine the critical chain length.

1. The ethyl homologues of the methonium series

In response to my request, partial progressive substitution symmetrically of ethyl for methyl terminations was made, using a chain length of four to seven inclusive methylene groups. This work was extended by the preparation of further homologues detailed subsequently.

2. The bisquaternary aminophenylalkylamines

In view of the work by Bovet upon simplifications of the tubocurarine molecule, it appeared to be useful to

investigate the substitution of a benzene ring for part of the methylene chain in the methonium series.

3. The pyrrolidinium compounds

The pyrrolidine ring occurs in a number of pharmacologically active substances, and the neuromuscular blocking properties of C.10 of the bis-pyrrole series were being studied by Taylor. The pyrrolidine ring offers a termination of physical size comparable with trimethylammonium, other shorter chain members of this series were made.

4. Morpholinium series

Chemical similarities are exhibited by three types of hetero cycles, pyrrolidine, morpholine, and piperidine. The piperidine series are known to have actions peculiar to the piperidine ring. A morpholinium series was made at the suggestion of Dr. Slack of the Organic Research Division.

5. The phenothiazine group

The phenothiazine ring has been employed in a series of antihistamines prepared by Bovet. One of these is promezathine (Phenergan) which is in use as an antihistamine. A homologue in which the nitrogen atom in the chain is quaternated was obtained from Rhone Poulenc.

6. Phenoxymethonium group

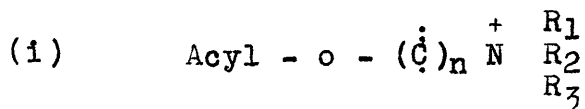
Phenoxydimethonium may be regarded as the C.1 of the series of which gallamine (Flaxedil) is the C.3. Bulbring

and Depierre have shown that it has greater sympathetic ganglion properties than gallamine. Phenoxytrimethonium was examined by Jacob and Depierre at the Pasteur Institute and their unpublished results were supplied by Professor Paul. It was found to have an activity equal to tetraethylammonium as a ganglion blocking agent.

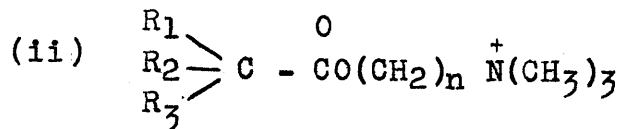
7. Synthetic atropine-like substances

In 1936 Ing prepared Lachesine which is a monoquaternary amine of aliphatic termination, which has been used by ophthalmologists in local application to produce mydriasis. No record existed of systemic dosage in man. The monoquaternary amines dibutoline and methantheline (Banthine) in use in America for the treatment of peptic ulceration, were also prepared for comparative examination.

8. From study of a number of antispasmodic and anticholinergic drugs, Dr. Wien of Biological Division suggested production of a number of monoquaternary amines as follows:-

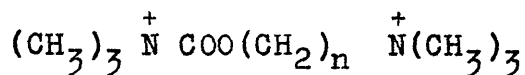


Alkaline esters of this type where C is a polymethylene chain or a cyclic structure as in the belladonna alkaloids, have a particular affinity for neural structures depending upon the nature of the acyl radical basic group, the polymethylene chain having not been studied beyond $n = 2$ or 3 .



where $R_1 =$ Phenyl or napttyl
 $R_2 =$ phenyl or H
 $R_3 =$ H or OH
 $n =$ 1 to 6

A bisquaternary series was also made upon his suggestion with a chain modification as indicated.



where $n =$ 1 to 6

The total number of new compounds which were made in the implication of this work was 180. They were examined pharmacologically and the methods used and the results where of interest are briefly described.

BIOLOGICAL RESULTS

Methods

It was necessary to establish techniques which would enable the toxicity and activity of the new synthetic compounds to be compared with drugs of known activity. In view of the number of new compounds, the use of simple techniques was desirable, e.g. gastric pouch preparations in dogs were not feasible. Of many possible techniques, the following four were adopted, and although the actions of some compounds were explored more fully, the results obtained by these four techniques were used as a basis for the selection of compounds for further use. It had to be taken into account that such biological methods of examination are not exact and that there is a considerable variation in individual and species response. Further, they were performed by relatively untrained staff working under supervision.

The four techniques used were as follows:-

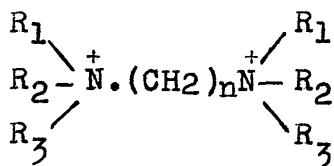
- T = toxicity in mice determined intravenously, the figures being in mg. per kg.
- S = the ganglion blocking activity on sympathetic ganglia, using the cat superior cervical ganglion preparation of Kibjakow (1933) as modified by Feldberg and Gaddum (1944).
- V = ganglion blocking activity of parasympathetic

ganglia using guinea pig ileum peristaltic reflex inhibition as described by Feldberg and Lyn (1949).

C = Curarising activity using the rabbit nerve diaphragm preparation described by Bulbring (1946).

For convenience the May and Baker numbers are used and the results obtained are as follows. The figures under the different activities are in terms of hexamethonium = 100, except in the case of curarising activity where d-tubocurarine = 100.

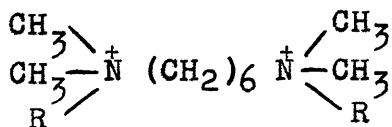
1. Ethyl homologues



No.	n	R ₁	R ₂	R ₃	T	S	V	C
1813	4	Me	Me	Me	122	1	5	0.01
2075		Et	Me	Me	61	10	25	0.01
* 2074		Et	Et	Me	35	100	25	0.01
2073		Et	Et	Et	20	5	5	0.01
1692	5	Me	Me	Me	62	65	75	0.40
2000		Et	Me	Me	16	150	150	0.40
2076		Et	Et	Me	-	125	100	0.40
1992		Et	Et	Et	8	7	10	0.40

No.	n	R ₁	R ₂	R ₃	T	S	V	C
1729	6	Me	Me	Me	60	100	100	0.50
*1863		Et	Me	Me	26	150	200	0.20
2031		Et	Et	Me	15	75	100	0.40
1993		Et	Et	Et	3	5	50	4.00
1847	7	Me	Me	Me	12	12	12	1.00
2163		Et	Me	Me	15	10	50	2.00
2164		Et	Et	Me	9	15	2	3.00
2165		Et	Et	Et	6	2	2	5.00

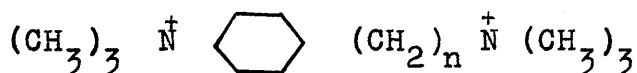
Compound 1863 was found in 1951 to be more active in man and further homologues were prepared as follows:-



No.	R	T	S	V
Hexa-methonium	methyl	100	100	100
* 1863	ethyl	220	150	200
1864	n-propyl	290	less than 5	less than 5
1865	isopropyl	270	15	10

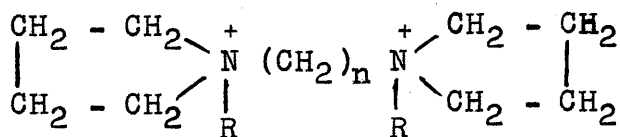
No.	R	T	S	V
1866	n-butyl	600	less than 4	less than 2
1867	isobutyl	250	less than 4	4
1868	allyl	260	4	4

2. The bisquaternary aminophenylalkylamines



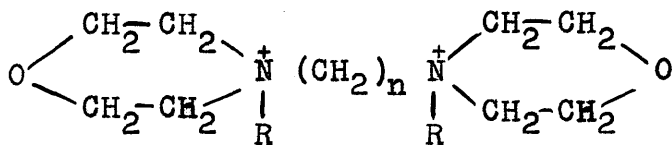
No.	n	T	S	V	C
* 1950	2	300	300	250	2
* 2034	3	-	25	100	-

3. The pyrrolidinium compounds



No.	n	R	T	S	V	C
*2050	5	Me	200	300	150	1
*2024	6	Me	350	250	150	1
*2060	6	Et	-	30	150	-

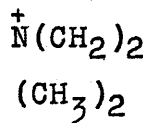
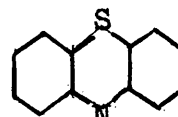
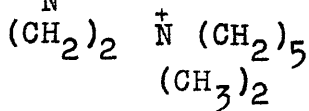
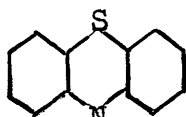
4. The morpholinium compounds



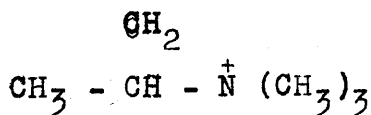
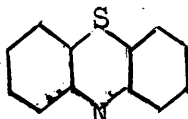
No.	n	R	T	S	V	C
* 2002	5	Me	33	100	100	2
* 1978	6	Me	66	100	175	4
1979	6	Et	-	6	20	-
* 2023	7	Me	400	100	33	-

5. The phenothiazine group

Rhone Poulenc
No. 3550

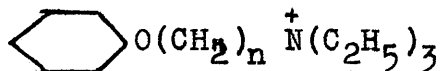


Rhone Poulenc
No. 3554



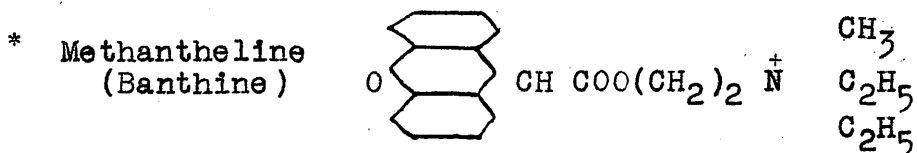
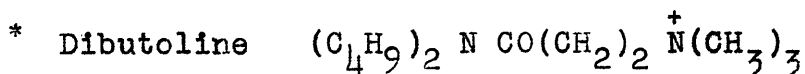
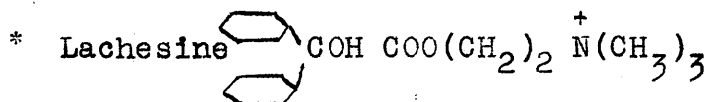
No.	T	S	V
* 3550	10	0	200
* 3554	5	50	1000

6. The phenoxymethonium group



No.	n	T	S	V
* 1826	2	6	10	200
* 1829	3	8	50	100

7. Synthetic atropine-like substances



8. No compounds of useful activity were obtained.

* These compounds were selected for clinical examination.

METHODS OF CLINICAL INVESTIGATION

Following selection of these drugs for examination, it was necessary to devise a procedure which would enable their effects upon the human autonomic nervous system to be compared. All the compounds were readily soluble in water and it was decided to administer them subcutaneously which would ensure absorption of all of each dose and yet would be a safer procedure than intravenous dosage in the event of unexpected toxicity.

The selection of patients occasioned some initial difficulty. The Royal Alexandra Infirmary is a hospital which is concerned entirely with the treatment of patients, and facilities for research are absent. Further, the rate of admission is such that it is not possible to allocate beds for a purpose such as this. I decided therefore, that the main part of the investigation should be performed upon a group of out-patients, the day-room of one male ward was available for this purpose for two or three mornings per week.

The production of severe hypotension is a risk to the life of elderly patients with hypertensive cardiovascular changes, and the administration of drugs, of potency determined by animal experimentation, capable of producing a fall in the blood pressure constitutes therefore an unjustifiable risk. From previous experience with hexamethonium

and M & B 1863, and from study of previous work such as that performed by Organe, Paton and Zaimis (1949), and Arnold and Rosenheim (1949), I decided that in the first place it would be desirable to administer the new compounds to subjects with normal pressures and absence of cardiovascular disease. As drugs affecting gastric secretion required identification also, a readily available source of suitable outpatients was found to exist in the form of young men between 20 and 45 years of age who suffered from duodenal ulceration, but were otherwise healthy. A group of 140 men between these years of age was collected without difficulty and the results of dosage of these drugs has formed the basis for subsequent work. It was found that these patients were agreeable to twice weekly morning attendance for a period of several weeks each. Later it was necessary to limit the group to 100 owing to various factors. One finding in patients with duodenal ulceration was a lower than average blood pressure, suggesting a higher level of vagal tone.

From various experience it was recognised from the commencement of this study that an individual variation in sensitivity to each drug was likely, and also it is necessary to take into account the possible development of tolerance during repeated dosage. Therefore, it was necessary to attempt to give all of these drugs in turn to each patient, and as far as possible they were given in different rotation.

It was to be expected that these drugs would modify all the functions of the autonomic nervous system. As the dosage required to demonstrate activity in the case of the new compounds was unknown, a small subcutaneous dose of the order of 2.5 mg. was administered first, and subsequently increased until hypotension or inhibition of gastric secretion to the point of achlorhydria occurred. In view of inconsistency in response, the dose which produced one or other of these actions in 60 per cent of observations was accepted as the effective dose. The observations recorded therefore, indicate the dose of each compound which was found to produce achlorhydria in 60 per cent or more of observations, or hypotension in this or more percentage of observations. In the case of some drugs, consistency of action to this standard could not be reached owing to the production of one or more side actions, and the dosage recorded was the effective dose upon the particular autonomic function involved.

As the drugs were available in a variety of inorganic and organic salts, dosage throughout is expressed in mg. of active cation.

Control observations

At different times patients were given injections of sterile water to provide control observations. No significant response occurred following this inactive injection. The patients were not informed upon which drug they were receiving

at any time. Intubation was a factor in modifying uncontrollably gastric secretion but this limitation applied to the first two or three observations only.

The following techniques were used:

1. Gastric secretion. The patients reported to the ward at 9 a.m. having had no food since the previous night. A Ryle's tube was passed immediately and the stomach emptied as completely as possible using the careful methods noted by Kay and Smith (1950). The Ryle's tube was left in position throughout the morning which was spent sitting reading and in quiet conversation with other members of the group which varied between six and ten patients. The stomach was emptied subsequently at hourly intervals i.e. at 10 a.m., 11 a.m., 12 noon and 1 p.m. The volume of the contents was noted, the pH was determined using a Marconi electrometer pH meter. Each specimen was then titrated with N/10 sodium hydroxide, using Topfers reagent to determine the free and total acidity as described in Clinical Methods (1949). The drug injection was made immediately after the 10 a.m. specimen was withdrawn.

There are no exact techniques for the measurement of gastric secretomotor activity. Swallowing a Ryle's tube and its presence in the stomach tend to inhibit or excite gastric secretion. Recently tubeless techniques have been developed, but these are inaccurate in quantitative studies of this type, their value lies in the detection of acid. The standard

fractional test meal described in Clinical Methods (1949) is unsuitable in that it provides a local stimulus to the oxyntic cell, while the action of the majority of the drugs used is a block in transmission at the higher level of the ganglion. The fasting acidity provides an indication of the basal tone of the parasympathetic nervous distribution to the stomach, and a modification of this level can be interpreted as an indication of the activity of a drug in blocking vagal ganglia, and enables the results to be compared with drugs which have an atropine-like action upon the peripheral synapse. Kirsner, Levin, Palmer, and others, arrived at this conclusion, and have used this method in investigating the activity of a series of mainly atropine-like synthetic compounds.

Owing to factors which influence the results obtained by aspiration of the gastric content, such as the patient's natural concern and the novelty of the experience, there is a tendency to consider that fractional test meal provide unreliable findings. In the course of this investigation it was found that by the second or third observation as a member of a group of patients with the same disease being subjected to routine examination, individual patients provided fairly consistent levels of fasting acid secretion of the order of 20 - 40 clinical units of free acid. Of the 140 patients, the results in 24 proved to be inconsistent even though they all suffered from proven duodenal ulceration. This group of

24 produced inconsistent results in the form of very low or very high levels of free acid and in some there were marked variations in the volume secreted. A further 16 patients failed to report following two or more observations and were therefore eliminated.

An asset in the conduct of this study was the symptomatic relief which attended the administration of a series of drugs which all affected the level of acid secretion to some extent. Within a period of a few months after this work ended, relapses occurred with recurrence of symptoms, and haematemeses or perforations in some cases.

2. Action upon the systemic blood pressure. Prior to and a half to one hour following injection of the drug or control injection, the blood pressure was recorded, using a standard mercury sphygmomanometer. The technique used was that recommended by the Committee of the American Heart Association (1939). The blood pressure was generally taken with the patient sitting upright on a hard chair. If dosage was sufficient to cause postural hypotension, the patient was assisted quickly to bed, and recumbent pressures then taken. Hexamethonium in sufficient dosage produced sudden loss of consciousness, while the syncope following administration of some of the newer drugs was of slower onset. The fall in the blood pressure of normotensive patients is not great in comparison with the fall which can be produced in the patients

with hypertension. If the original pressure is of the usual normal level of approximately 120/80 mm., full dosage of a ganglion blocking agent sufficient to produce maximum vasodilation is followed by a fall in the blood pressure when the patients are recumbent to 60/80 mm. systolic and 40/60 mm. diastolic. This proved to be sufficient for patients to maintain consciousness feeling no ill effects. Raising the head produced loss of consciousness. At no time was a pressor agent required for treatment and this was mentioned by myself and Campbell (1953). Previously some deaths have followed repeated dosage of adrenaline to relieve hypotension. The correct antidote is noradrenaline and a supply of this pressor amine was kept ready for use.

The systolic and diastolic blood pressures were recorded to the nearest 5 mm. of mercury. Drugs having a definite hypotensive activity were given in dosage sufficient to produce a fall in the diastolic pressure of 20 mm. or more and the side effects with dosage of this magnitude were recorded.

Pulse Rate

The pulse rate per minute was recorded immediately before and one hour following drug injection, any alteration in the rate following a postural fall in the blood pressure was also noted.

Peripheral Blood Flow

The fall in the blood pressure produced by ganglion

blocking agents is due to blockade of sympathetic ganglia with resulting decreased arteriolar tonus, an increase in peripheral blood flow occurs. In view of the possible application of these drugs in diseases with sub-normal peripheral flow, it was decided to investigate the extent which the peripheral flow was increased by the new compounds. A number of methods are available, the optimal digital plethysmograph constructed by Goetz was used to further the studies upon pentamethonium by Arnold and Graham (1949). For the purpose of this investigation a simple method was required by which relative alterations in peripheral blood flow could be determined, the degree of accuracy of the technique being unimportant compared to relative changes. Of the methods available, estimation of the skin temperature was the most suitable. Although many factors are involved, the temperature of the skin of the foot is lower than that of the skin at the umbilicus, mainly due to the cooling which takes place during the flow to the periphery. This is known as the umbilical-toe temperature gradient. If the blood flow is increased, the gradient is decreased. The numerous circumstances which may affect the accuracy of results have been described by Sheard (1944). Another useful method of expressing increase in peripheral blood flow is the Thermal Circulation Index. This Index is directly proportional to the change in the blood flow. Burton (1940) has shown that figures as high as 12

can be recorded for the toes, indicating an increase in peripheral circulation of twelve times, the maximum change between full vaso-constriction and full vaso-dilation. From his nomogram, the Thermal Circulation Index is readily determined if the rectal, room, and toe temperatures are known. Ideally, a constant room temperature of 20°C is required, the patient resting unclothed for a sufficient period to stabilise his heat production and losses. The hospital ward dayroom provided a constant temperature throughout the period of observation, but it varied from day to day between 16°C and 20°C. Experiments were made permitting the patients to remain in normal indoor clothing, when it was found that a temperature gradient of approximately 9°C was obtainable. This gave a Thermal Circulation Index of approximately 1.0, compared with 1.5 to 2 with the patient unclothed, but this is of a magnitude sufficient to interpret changes which were up to an Index of 3 following drug action.

Stewart (1930) has shown that a cork insulated thermometer is accurate to within 0.5°C. The better method is a thermocouple, but this apparatus involves the use of a galvanometer of high voltage sensitivity, large in size, and insufficiently robust for routine use. Another sensitive method is a resistance thermometer, the principle involved being the change in resistance of a ferro-nickel alloy wire with alteration of temperature. Recently thermistors have

been employed and a series of Stantel thermistors were connected in a Wheatstonebridge circuit using a Baldwin galvanometer. Accurate readings were possible with this instrument, the small contact area and thermal capacity of the thermistors being ideal for the purpose. However, this apparatus proved to be too delicate for routine use in the large number of observations required, and it was subsequently used to check the readings of a thermometer sensitive to 0.1°C . As described by Stewart, the thermometer bulb was held in a cleft cut in a small cork with the exposed portion against the skin. An accuracy of better than 0.5°C was obtained which was more than adequate for the purpose.

It is to be emphasised that no attempt was made to obtain absolute results. The variations in skin temperature before and after drug dosage were recorded to provide a comparison of actions, as these variations may be approximately correlated to alterations in the peripheral blood flow.

Mydriatic and Cycloplegic action

The pupil size was noted before and one hour after each drug injection, the diameter of the right pupil being measured with a transparent calliper to the nearest mm. The results have been recorded, together with the average changes in diameter. An uncontrollable factor was found to be the room brightness, bright sunshine invalidating measurements. Accurate measurement of cycloplegia is difficult.

A readily applied method such as that described by Kirsner et al (1952) was found to be no more accurate than the inability of the patient to read small print. This complaint was noted.

Sweat Gland Activity

Carmichael et al (1941) have examined the methods of measurement of sweat gland activity by determination of the skin resistance. For this purpose a Taylor Model No. 95A meter was used with 1 cm² electrode at a potential of 10.5 volts. The results were expressed in kilohms with the average ratio of the readings before and after drug injection.

Salivary Gland Activity

Complaints of dryness of the mouth were noted, a standard technique such as mastication of 3.5 g. of solid paraffin and collection of saliva as described by Levin et al (1952) being regarded as unnecessary.

Effect on Respiration and Curarising Activity

These new drugs are closely related to powerful curarising agents and their study in animal was insufficient to determine if they possessed central depressant properties. The respiratory rate was therefore measured and careful examination made to determine any muscular weakness following drug administration. Neither effects were encountered, but as will be recorded subsequently, one group of drugs produced some central depression.

CLINICAL RESULTS

The clinical results of the initial examination are appended, and further observations are detailed in a reprint and a copy of an article awaiting publication.

The actions of these compounds in man may be summarised as follows, atropine has been added to give a comparison with this drug as well as with hexamethonium:-

Compound	<u>Sympathicolytic action</u>			<u>Vagolytic action</u>			
	B.P.	R.G.	R.T.I.	G.	P.	P.R.	S.
Hexa-methonium	50	2.1	2.00	50	1.4	8.8	2.70
1. 1863	20	1.4	1.37	18.5	0.4	8.4	2.22
2074	75	0.5	0.87	12.5	0	0.8	2.08
2. 1950	15	1.0	1.31	50+	2.2	11.2	1.54
2034	35+	0.2	0.90	40+	-0.4	0.8	1.97
3. 2050	5	2.4	2.08	12.5+	4.0	17.6	1.31
2024	50	0.6	1.16	12.5	0.6	4.0	2.45
2060	45+	1.5	0.97	60+	0.2	7.6	2.47
4. 2002	10	0.4	1.25	35+	0.8	12.8	2.03
1978	15	0.8	1.44	50+	0.8	3.6	1.93
2023	50	0.9	1.00	75+	1.8	1.2	2.22

Compound	Sympathicolytic action			Vagolytic action			
	B.P.	R.G.	R.T.I.	G.	P.	P.R.	S.
5. 3554	-	0.3	0.98	30.0	1.2	34.4	3.16
3550	-	+1.1	0.66	150+	-0.6	5.6	1.30
6. 1826	-	0.5	1.15	100+	-0.2	-6.0	1.07
1829	150+	0.9	0.83	150+	-1.2	-6.0	1.08
Atropine	-	0.1	0.85	2+	0.8	4.0	2.06
Lachesine	-	1.1	1.05	10.0	2.6	9.4	2.38
7. Dibutoline	-	0.1	1.16	40.0	1.8	20.0	3.52
Methantheline	-	0.8	0.8	50.0	0.6	35.2	5.50

B.P. = mg. subcutaneous dose of cation required to reduce the blood pressure.

R.G. = degree centigrade reduction in the umbilical toe temperature.

R.T.I. = reduction in Thermal Indices.

G. = mg. cation subcutaneous to inhibit gastric secretion.

P. = increase in pupil size in mm.

P.R. = increase in pulse rate per minute.

S. = ratio of skin resistances, the higher numbers being a decrease in sweat secretion.

* = inconsistent action in this dosage.

Analysis of Action

1. The ethyl homologues of the methonium series

The general activity of hexamethonium upon autonomic function has been demonstrated. 1863 is a more active drug. In contrast to the pharmacological results, 2074 has a predominance of action upon gastric secretion of almost 4 - 1.

2. The bisquaternary aminophenylalkylamines

1950 is an active sympathicolytic agent with less effect upon gastric secretion. It produces mydriasis.

3. The pyrrolidinium compounds

2050 is the most active of the drugs used in depressing blood pressure, producing a fall in dosage comparable with the effective dose of decamethonium as a curarising agent. It is more active upon the blood pressure than upon gastric secretion, but it is a marked mydriatic. 2024 is active upon gastric secretion in dosage a quarter of that required to affect the blood pressure.

4. Morpholinium series

2002 and 1978 are sympathicolytic agents more active than hexamethonium.

5. The phenothiazine group

3554 has an atropine-like action and produces tachycardia. 3550 depresses gastric secretion with a minimum of other actions, but it is relatively inactive, the increase

it produces in the Temperature Gradient is the hypothermic property of antihistamines containing the phenothiazine ring.

6. The phenoxymethonium group

1829 was remarkable in tending to produce a slight elevation of the blood pressure.

7. Synthetic atropine-like substances

The marked atropine-like side actions of this group which limit their clinical application has been confirmed. Methantheline produced the greatest effect in suppressing sweat secretion, it is used for this purpose. The dosage used of atropine was insufficient to produce marked actions. The effects of this alkaloid were inconstant in this dosage.

Selection of drugs

Of the drugs investigated, 2050 (pentapyrrolidinium) was the most active in reducing the blood pressure, and in the dosage required to do this, side effects other than mydriasis are not marked. As a sympathicolytic, it may be compared with hexamethonium. 2024 (hexapyrrolidinium) and 2074 (ethyltetramethonium) suppress gastric secretion in dosage less than required to reduce the blood pressure, they may be compared with methantheline (Banthine).

Comparative activity (hexamethonium = 100)

<u>Compound</u>	<u>Sympathicolytic</u> blood pressure	<u>Vagolytic</u> gastric secretion	<u>Side Effects</u> mydriasis dry mouth tachycardia
Hexamethonium	100	100	100
pentapyrrolidinium	1000	800	150
hexapyrrolidinium	100	800	50
ethyltetramethonium	150	520	50
methantheline	inconstant	100	150

During repeated dosage of these drugs, it was found that hexapyrrolidinium produced some cumulative effect upon the blood pressure, drowsiness and depression occurred. Further studies were concentrated upon ethyltetramethonium.

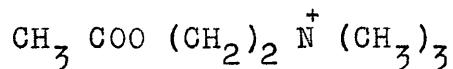
Two drugs have been produced offering advantages over known synthetic compounds affecting synaptic transmission. Pentapyrrolidinium (2050) is 10 times as potent in depressing the blood pressure as hexamethonium, the increase in vagolytic activity being less marked, and the main side effect being mydriasis.

Ethyltetramethonium (2074) is 5 times as active in suppressing gastric secretion than hexamethonium and methantheline, its side effects are less.

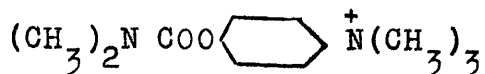
They are both ganglion blocking agents.

DISCUSSION

Comparison of the results obtained with the clinical pharmacology of other new compounds described and quoted from the literature suggest the consideration of a number of hypothesis. It appears to be a reasonable possibility that the quaternary ammonium grouping is the point of attachment of a chemical transmitter at the receptor site. If the molecule of acetylcholine is examined, it is seen to consist of this quaternary ammonium grouping, a chain of significant length, and a transmitting termination.

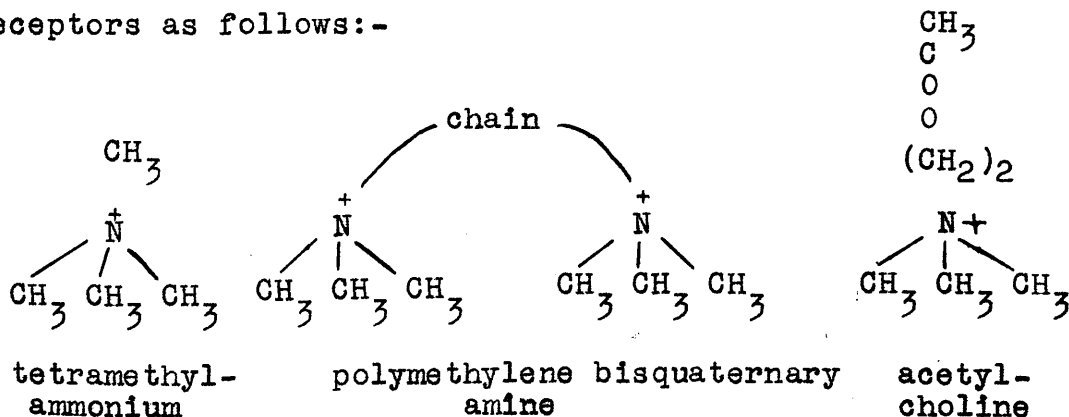


It has been postulated that cholinesterase inhibits acetylcholine by hydrolysing it, evidence supporting this having been produced by Marnay and Nachmansohn (1938), altering the transmitting termination to acetic acid, the remainder being inert choline. However the studies of Burgen (1949) have suggested that the negativisation of acetylcholine takes place more rapidly than a chemical hydrolysis can account for, and a physical combination of acetylcholine with cholinesterase is perhaps the method of inhibition. It is possible that this is the explanation of the action of cholinesterase inhibitors such as Prostigmin.



As can be seen from its formula, it bears a close resemblance to acetylcholine, so that it may saturate cholinesterase. Prostigmin itself has cholinergic activity beyond that due to cholinesterase inhibition as has been shown by Riker and Wescoe (1946), using di-isopropylfluorophosphate. This action is perhaps due to the carbamate grouping which it has in common with physostigmin, which may in some cases operate similarly to the transmitting end of acetylcholine itself.

It is possible to suggest that tetramethylammonium and tetraethylammonium act by virtue of comprising the end attractive to the receptor site of acetylcholine and some endorsement is given to this by the demonstration of Barlow and Ing (1948) that the bisquaternary lower members of the polymethylene series have twice the blocking activity of these monoquaternaries, suggesting occupation of two receptors as follows:-

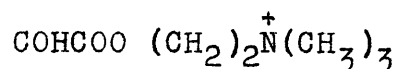


These monoquaternaries, tetraethylammonium and tetramethylammonium have differences in sites of action in the distribution of the autonomic nervous system, the former having a predelection for the sympathetic ganglia, and the latter for the neuromuscular junction. It is difficult to explain such differences in action other than a basis of differences in the receptor sites. In their early work, Dale and his colleagues, rather than suggesting that acetylcholine is the specific chemical transmitter at the autonomic ganglia, parasympathetic post ganglionic transmissions and neuromuscular junctions, identified it as the most active cholinergic compound; and it is possible that instead of acetylcholine being the key which opens all synapses to the action potentials, it is to be regarded as a master key which will perform this function in the relatively high dosage which has been used in pharmacological experiments, the actual physiological transmission being due to the reorientation of quaternary amine complexes in response to alterations in actions potentials. Whatever the mechanism, it appears that as far as the receptor site is concerned, the physical fit is more important than the chemical structure, i.e. it is the quaternary ammonium shape and possibly its positive charge which determines the fit and adhesion.

Studies of molecular structures resembling acetylcholine have not been extensive despite the work of Dale and his colleagues who showed that differences in the distribution of preponderance of action occur in esters and ethers of choline. The cholinesterase inhibitors were discovered following the fundamental work by Stedman and his coworkers who published between 1926 and 1933 the results of their examination of the methyl carbamic ester grouping $\text{CH}_2\text{NH COO}$, leading to the discovery by Aeschlimann and Reinert (1931) of Prostigmin.

On the other hand, in the United States the problem of peptic ulcer has occasioned a large volume of study upon synthetic substances of atropine-like action. This course of action has been defined by Beattie (1949) who, reviewing the possibilities of treatment of peptic ulceration, has stated that it should not now be beyond the limits of future possibilities for suitable drugs to be developed to control the vagotonia which is the underlying cause of the ulcer diathesis. Studies have been made of the tropine-tropic components which resulted in the production of monoquaternary amines such as methantheline (Banthine) and later S.C.3171 (Pro-Banthine). The latter is B-diisopropylaminoethyl xanthene-9-carboxylate methobromide, a monoquaternary amine. It has an action closely similar to that of atropine. In 1936 Ing produced monoquaternary amines of

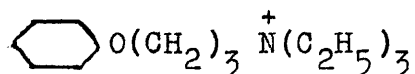
similar action recording studies of the one of these used in this work, Lachesine. The structural formula is as follows:-



It will be seen that these compounds closely resemble acetylcholine in having a quaternary ammonium termination which fits the receptor site and a methylene chain; but the transmitting end of acetylcholine is replaced by the structure which does not permit of a response to the action potential. The further work in the United States upon compounds such as Prantal, Darstine, and Pamine, shows that these compounds have similar actions. The studies which have been recorded here upon Banthine and Lachesine confirm this atropine-like activity and this has been shown also by 3554 R.P. (thiazinamium) which is the antihistamine promezathine with quaternation of the side chain nitrogen atom, suggesting the possibility of a basic mechanism of antihistamine/chemical transmission activity. Compound A.Y. 5212 studied by McKenna et al (1954) is also based upon this phenothiazine nucleus.

From these results it appears that monoquaternary amines resembling acetylcholine except in regard to the transmitting termination, will produce inhibition at the parasympathetic postganglionic transmissions. However the American literature, as will be shown later, indicates that the new

monoquaternary amines they have produced are unsatisfactory for the treatment of peptic ulceration in that their side effects have been identical with those of atropine, except tachycardia which has been less pronounced. This work continues in the hope of finding a selective synthetic compound of atropine-like activity confined to gastric secretomotor distribution of the parasympathetic nervous system. A series of monoquaternary amines were examined (1823, 1825, 1826, 1829), the last two being recorded. The close resemblance to acetylcholine is evident except in the transmitting termination, the acetylcholine grouping being replaced by a benzene ring. Of these, M & B 1829 proved to be the most active in suppressing gastric secretion. Its structural formula is as follows:-



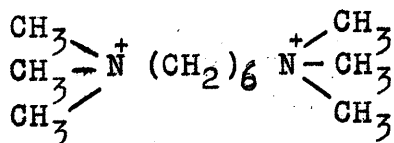
Unfortunately this monoquaternary amine was relatively inactive compared with other compounds. Dosage as high as 100-200 mg. of cation subcutaneously was required to demonstrate action upon gastric secretion and the latter dose required a volume of injection of 10 c.c. which was impractical for more than a few doses. The action of this compound was remarkable in that side actions of atropine type were absent. Professor Bain of Leeds has examined the methyl homologue which appears to have some

activity in inhibiting amine oxydase, confirming a small but consistent rise in the blood pressure which followed dosage of this drug.

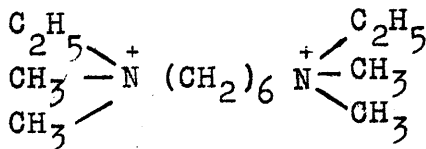
In summary it may be stated that monoquaternary amines, resembling acetylcholine in having a quaternary termination to occupy the receptor site, a chain of definite length, and terminations of various types, resemble atropine closely in their actions in man and are therefore subject to the limitations of atropine when used to inhibit gastric secretomotor activity. However many variations of these compounds have been produced and it is possible that eventually a more selective action will be obtained, especially in that such a selectivity of action has been demonstrated with M & B 1829, unfortunately in a relatively inactive compound.

Examination of the homologues of the polymethylene bistrimethylammonium series reveals a number of points of interest. The ethyl homologues, which represent quite small variations in the molecular structure, exhibit remarkable differences in activity. Two compounds of special interest which have been examined are M & B 1863 (Gaplegin) and M & B 2074 (ethyltetramethonium). The formulae in comparison with hexamethonium are as follows:-

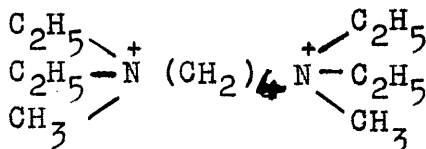
Hexamethonium



Gaplegin



Ethyltetramethonium



The monoethyl homologue of hexamethonium, Gaplegin, shows increase in potency which was determined by Campbell, Graham, and myself (1952) and confirmed by Smirk (1952). The increase of activity was insufficient to afford advantage over hexamethonium and this drug tended to have some vagal preponderance of action manifested by constipation. This ethyl homologue of C.4 shows the need for examination of a series of different molecular lengths in that this active compound is based upon tetramethonium which is relatively inactive, the increase of effective length presumably being due to the greater orbit of the extra two carbon atoms at either end. It is to be noted that a preponderance of sympathicolytic activity was found in the biological investigation, and this compound was examined first from this viewpoint. Further biological studies reversed the previous verdict, the results subsequently being in accord with the clinical findings. This experience in particular, emphasises the need to perform in man as broad a survey as

possible of new drugs, as the results of animal experimentation are not necessarily reliable.

The activity of the morpholine and pyrrole homologues tends to afford a suggestion that the molecular shape is more important than the chemical structure of the receptor termination. Pentapyrrolidinium has been shown to have a high degree of activity and to act mainly upon sympathetic ganglia to an extent beyond that predictable from animal experimentation. This action in man has been described by myself and Campbell (1953) and this compound is now being used in the treatment of hypertension.

From the results obtained with the bisquaternary homologues of the methonium series, it is possible to suggest that effective ganglion blocking agents are obtainable by using different types of quaternary ammonium terminations, and variants may be more potent than the original series, possibly due to increased difficulties in detoxication. The chain length is critical, and the results tend to confirm the hypothesis that the physical fit is the criterion of ability to block the receptor sites. Study of the sulphur homologues was not performed, but subsequent work will probably extend confirmation of these hypotheses.

The polymethylene series are unique in the simplicity of their methylene chain which represents a relatively inert method of spacing the quaternary terminations at an optimum

distance. There are numerous possibilities of alterations in the chain structure including a modification of potential activity such as the type found in compound 2268F which has been shown by Bovet to be a profound cholinergic. Of many possibilities, it appeared to be most interesting to continue the work of Bovet in the studies of the tubocurarine molecule. Accordingly, a series of compounds were made incorporating a benzene ring in the methylene chain, accepting a length of four carbon atoms for the benzene ring. As was expected the dimethyl compound of this series was of high ganglion blocking activity and although not as potent as pentapyrrolidinium, it was more selective in depressing the blood pressure. Its duration of action was shorter than that of pentapyrrolidinium. The 4th and 5th members of this series are very active curarising agents.

CONCLUSIONS

- 1) Examination of the actions in man of a number of bis-quaternary amines and monoquaternary amines has indicated that the former are ganglion blocking agents, while the latter mainly affect the peripheral parasympathetic synapse.
- 2) Bisquaternary amines active in blocking autonomic ganglia may show differences among themselves in affecting vagal and sympathetic functions, comparable with differences observed and recorded among monoquaternary amines and alkaloids.
- 3) From the differences in activity upon various functions of the autonomic nervous system found in this range of compounds, it is possible to advance tentatively a suggestion that these various functions are mediated through different types of synapse.
- 4) The polymethylene bistrimethylammonium series form a useful basis for new compounds with significant modifications to the chain or terminations. By such modifications, new compounds with variations in distributions of activity, and of a greater potency and duration of action can be produced. The physical fit of the termination in the receptor site may be more important than the chemistry.

- 5) Bisquaternary amines with a suitable distribution of activity offer a better prospect in effecting a block of vagal transmission than the monoquaternary amines so far produced, in that their side actions may be less troublesome.
- 6) The production of new ganglion blocking agents is of value not only in extending knowledge of synaptic functions, but in producing drugs of potential usefulness in the treatment of some diseases, drugs such as pentapyrrolidinium and ethyltetramethonium.

SECTION II

In this section, the application of the new synthetic ganglion blocking agents, developed as recorded in the first section, in the treatment of hypertension and peptic ulceration is described. The place of these drugs in therapeutics is discussed.

In 1915 Eppinger and Hess envisaged a state of sympathetic or vagal overactivity, ascribing a number of disorders to this state. Research into the mechanisms involved in the production of hypertension and peptic ulceration has revived interest in their postulates.

The activities of the autonomic nervous system are manifold and complex, in that this part of the central nervous system is concerned with the maintenance and regulation of a large number of body functions, forming a basic nervous control superimposed upon the phylogenetically more primitive humeral mechanisms, and embodying chemical methods of propagation of activity.

The lower motor centres of autonomic activity are probably located mainly in the floor of the fourth ventricle. There is a higher level of control at the hypothalamus, and these hypothalamic centres may act by coordination of autonomic nervous activity with the humeral control exerted by the pituitary gland. It is probable that the hypothalamus is a coordinating and relay station, rather than the highest level of control. Recently Chapman (1954) has demonstrated fluctuation in the blood pressure following

electrical stimulation in the region of the amygdaloid nucleus, showing that these fluctuations occurred without subjective response such as followed the placing of the electrodes upon other parts of the temporal, or upon the frontal lobes. The highest centre of control of gastric secretion so far postulated is in the hypothalamus, as Illingworth (1953) has noted; but it is probable that a higher centre lies at a level comparable with that of the amygdaloid nucleus, which lies between the tail of the caudate nucleus of the basal ganglia and the temporal cortex, being continuous with the grey matter of the latter.

Of the conditions which Eppinger and Hess have postulated are due to autonomic overactivity, the causation of hypertension and peptic ulceration offers a possibility of explanation by their hypothesis. Unfortunately the mechanisms involved in the causation of these diseases are more complex than a simple and unexplained response to excessive nervous tone. It is important to review what is known of the mechanisms of production of these diseases, in order to determine the place in therapeutics of procedures which will interrupt autonomic nervous tone.

MECHANISMS INVOLVED IN THE PRODUCTION OF HYPERTENSION

The essential mechanical factors concerned in the determination of the blood pressure are the cardiac output, the volume and viscosity of the circulating blood, and the peripheral resistance which is a function of the calibre of the arterioles. The pressure levels are modified by the elasticity of the major arteries including the aorta. As Wood (1952) has expressed it, there is a division of hypertension into two categories, a systolic bias and a diastolic bias. The upper level of normal blood pressure quoted by Wood is 150/90, and a rise in pressure above this constitutes hypertension of a systolic or diastolic type depending upon which of the pressure levels is more increased.

Systolic Hypertension

The forcible ejection of blood by the contracting left ventricle causes a wave of pressure throughout the arteries constituting the systolic blood pressure. This is modified by the elastic recoil of the aorta and major arteries, and to a less extent by the arterioles of medium calibre. The systolic blood pressure is increased relative to the diastolic pressure if there is an increase in cardiac output in the form of rapid forceable ventricular contraction, and therefore a systolic hypertension is found physiologically following exertion, and in response to sympathicomimetic drugs such as ephedrine which increase the heart rate. Pathologically it

occurs in thyroid overactivity. Of importance is the systolic hypertension due to the loss of arterial elasticity. With advancing years, arteriosclerotic changes develop and result in systolic hypertension which does not in itself constitute an impairment to life expectation, but places a strain upon the left ventricle, and in some cases, reduces the blood flow to the extremities, so that arterial degenerative changes of this type are often followed by intermittent claudication. In that the causes are mechanical, there is little opportunity for prevention and treatment of the systolic hypertension of arteriosclerosis, which is probably predisposed to by constitutional and hereditary factors. However, the condition is generally benign and compatible with a good life expectation.

Diastolic Hypertension

Diastolic hypertension is due to an increase in the peripheral resistance so the arterial blood flow is restricted during passage through the arterioles, with resulting elevation in the basic or diastolic level of the blood pressure. This control is under the influence of the sympathetic nervous system. The motor impulses relay in the paravertebral ganglia, and are distributed by the arterial sympathetic plexi. Little is known of the afferent pathways and mechanisms by which the balance of vasodilation and constriction is maintained, and the peripheral sympathetic synapse remains to be

elucidated except in so far as the functions of the sympathathins are becoming progressively better understood. Until 1946 the action of the sympathathins was regarded as due to the secretion of adrenalin or to the release of adrenalin from centres such as the adrenal medulla. In that adrenalin was regarded as the prime peripheral sympathetic chemical transmitter, many anomalies appeared during attempts to interpret sympathetic activity. Some of these inconsistencies were explained by a sensitivity to acetone which tends to be present in solutions of adrenalin. It was not until study of the pressor amines resulted in the discovery by Euler in 1946 of noradrenalin, that a more accurate study of sympathetic activity was made possible.

It is of interest to examine some of the known mechanisms of control of the diastolic blood pressure.

Mechanisms of control of the blood pressure

The level of the blood pressure in the individual is predetermined by constitutional and hereditary factors as has been shown by Platt (1950), and in the subsequent statistical studies of Pickering (1954). The normal blood pressure centres around the level of 80 mm. diastolic pressure and in the determination of this average there exists a proportion of the population with diastolic pressures of higher levels constituting essential or benign hypertension. It is probable that the centre for this control is, as Merrill has

suggested, in the hypothalamus; and that the control is exerted by influence over the secretions of anterior pituitary, with its actions upon the suprarenal cortex in controlling salt and water metabolism, thus determining the intravascular fluid volume and its relation to the extravascular fluid content; and through the medullary centres controlling heart rate and response to body requirements. From an early date, an emergency mechanism has been recognised by which in response to upper centre stimuli in the form of powerful emotions, adrenalin is secreted by the adrenal medulla; resulting in both systolic and diastolic hypertension provided by increase in the cardiac output and deviation of blood flow from the skin, kidneys, and digestive tract to skeletal muscle in order to provide a maximum output of physical energy under conditions such as a primitive anxiety of preservation of life by flight. The extent to which adrenalin is responsible for control of the blood pressure under normal circumstances remains to be determined, but it is probable that a basic level of adrenalin secretion by the suprarenal medulla is of less importance in this function than secretion of noradrenalin. It is the function of the latter to govern the moment to moment changes in pressure and the blood flow requirements of different organs by producing vasoconstriction of the arterioles.

There is a reflex mechanism of control of the pressure level by the carotid sinus. Dilatation of this sinus produced

by a rise in blood pressure influences receptor organs within its wall, motivating vagal activity to lower the arterial pressure. The site of the carotid sinus in the arterial pathway to the brain is to be noted. It is possible that this was determined by a necessity to protect the relatively unsupported cerebral vessels from extreme rise in pressure. Such receptor organs are also found in the aorta and major arteries, and as will be commented upon later, Euler (1954) has suggested that interference with these may be followed by hypertension.

A further measure of control is provided by the kidneys in that a filtration head of pressure is required at the glomerulus to ensure the mechanical process of dialysation. Insufficient pressure in the afferent arteriole, as has been shown by the renal ischaemia experiments of Goldblatt (1934), is followed by the secretion of pressor substances which combine with dihydroxytryptamine to increase the systemic blood pressure and thereby improve the renal blood flow.

In the production of hypertension in man, examination of these circumstances shows a possible aetiology as follows:-
Renal Hypertension Wilson (1953) has described in detail the involvement of chronic glomerulo nephritis in the production of hypertension. It is a common termination and anomalies of the kidney. Chronic pyelonephritis is probably fairly common causes of hypertension, in the female especially, and in that

the disease may be unilateral, there exists a theoretical possibility for treatment in the form of excision of a diseased kidney. Pickering and Heptinstall (1953) have recorded successful results following this operation, but the total number of cases described in the literature is 53, and although the possibility of this treatment is not to be ignored, the instances in which it can be used are limited. Indeed, Smith (1948) has stated it is unjustifiable to perform neephrectomy in order to control hypertension except in circumstances of indication for this operation because of renal disease, in that by extirpation of a kidney in which there may be surviving tissue capable of function, the possibility of renal failure is increased.

The Carotid Sinus The distensibility of the carotid sinus decreases as arteriosclerosis progresses with age, and Euler (1954) considers that this may be an important consideration in the development of hypertension, especially in the presence of atherosclerotic changes which may involve the receptor organs. Thus hypertension of a small degree during early life may produce such changes and lead to an accelerated form of the disease.

Humeral Pressor Substances

It is difficult to assess to what extent serotonin is implicated in the production of renal hypertension in man. However, the information upon this substance has been greatly

extended by the identification of Rapport et al (1948) of serotonin as hydroxytryptamine which is the amino acid tryptophan with a hydroxy group attached to the ring.

Further studies have been made in an attempt to find antagonists, and Wooley and Shaw (1954) have produced a series of compounds resembling hydroxytryptamine, which antagonise their actions presumably by selective competition. One of these, medmain, inhibits the effect of serotonin on smooth muscles, while some related compounds prevented the rise in blood pressure caused by serotonin in dogs, being described by them in 1953. So far these drugs have not been used in man because of their action upon the central nervous system, probably occasioned by inhibition of amine oxydase in the brain.

The Suprarenal Medulla Tumours of the suprarenal medulla and of ectopic chromaffin tissue, the glands of Zuckerkandl, may produce hypertension by secretion of adrenalin and of noradrenalin, which is characteristically paroxysmal, but may become fixed.

The Suprarenal Cortex The observations by Cushing (1934) upon basophil adenomata of the anterior hypophysis with cortical stimulation led to the implication by Merrill (1952) and others, of what they described as the "pituitary-adrenal axis" in the production of hypertension. As Page (1949) has observed in his review of the experimental methods of production of hypertension, that induced by dosage of D.C.A. (desoxycorticosterone

acetate) resembles most closely benign hypertension in man. As Wolfarth et al(1951) have shown, the adrenal cortex has a more fundamental importance in producing and sustaining hypertension than the sympathetic nervous system, but Merrill (1953) has demonstrated that removal of both suprarenal glands will not control hypertension, while Page has concluded that the only method of restoring experimentally induced hypertension to normal levels is excision of the pituitary gland.

Further information upon the possible action of D.C.A. has been given in the preliminary communication by McDowall and Solinan (1954). Their studies have been concerned with their finding that sodium accumulation occurs at specific receptors following upon dosage of blocking drugs such as mepyramine and atropine, and this state may be reversed by certain other drugs. It is suggested that blocking agents may prevent a temporary sodium shift in response to the action potential demonstrated by Hodgkin and Katz (1949). It is possible to deduce that D.C.A. exerts a control over the cellular sodium extrusion manifested by its known action in maintaining body sodium. The hypotension produced by adrenalectomy is reversible by increasing the dietary salt intake.

While these findings have a place in the consideration of the mechanisms involved in the production of hypertension, they do not explain the pathogenesis of the disease in its

common form in man, essential hypertension, the aetiology of which remains obscure. There is little doubt regarding the marked hereditary predisposition confirmed by Platt (1947), although his survey was based upon pressure levels, and did not take into consideration the development of signs and symptoms of hypertension. Master et al (1943) have shown elevation of the blood pressure is extremely common, being found in 30% of males and 40% of females over 40 years of age. Hypertension in itself does not necessarily constitute a threat to life, and the prognosis which has been reviewed by Leishman (1953) is generally indeterminate. The studies by Bechgaard (1946) have shown an increasing rise in the diastolic pressure with age. However Kean and Hammill (1949) have found that this rise does not appear to occur among the primitive tribes they examined, and they were tempted to suggest that the stresses of civilisation are reflected in the production of hypertension. Certainly during the stress of prolonged periods of warfare in the Western desert, transient hypertension occurred as Graham (1945) has described. Gavey (1954) has provided an indication that under circumstances of long continued stress, rises which were at first transient, may become permanent. It is possible that part of the hereditary predisposition may be constituted by a tendency for an individual reaction to environment. Wolf et al (1948) found that there was a high incidence of obsessive compulsive traits and subnormal assertiveness among patients with

hypertensive vascular disease. The reaction of these patients to the threats and challenges of every day life were suggested by Gressell et al (1949) to be restrained aggression, with a vascular component of elevation in the blood pressure and renal vasoconstriction. Merrill (1952) has attributed development of essential hypertension to psychic stimuli with adrenal activity in response to hypothalamic stimulation.

As Page and Wilson have stated, it is not readily possible to correlate experimental production of hypertension with the disease as it presents in the human. Some of these mechanisms are recognisable, but the great majority of patients suffer from essential hypertension of obscure aetiology. It is exceptional for psychic factors to be obvious. Patients are occasionally encountered in states of anxiety and depression who have hypertension, but hypertension is an uncommon complication of neuroses and psychoses. Psychiatric investigation of hypertensive patients is rarely indicated, but the mental factors aggravating or causing the hypertension may not be obvious to the physician, nor may they be of a severity sufficient to merit investigation. It may be that we have to accept the presence of such factors in some patients leading apparently normal lives. In essential hypertension there may be constitutional tendency for the slow rise in the diastolic pressure over a period of many years with, in the

majority of patients, a benign course which does not curtail the life expectation. Perhaps during periods of stress, transient elevations in the blood pressure occur, possibly due to a modified reaction on the part of the adrenals - the emergency mechanism. If these periods of hypertension are repeated sufficiently often, a more basic mechanism, probably the pituitary-adrenal axis, resets the diastolic blood pressure at a higher level to be more in accord with the requirements of the individual, and in turn adrenal stimulation leads to a vicious circle of increasing pressure. Alternatively and perhaps simultaneously, atherosclerosis of the aortic and carotid centres sensitive to changes in pressure level may destroy the reflex regulation mechanism. As will be discussed subsequently, the actual level of the resulting hypertension is of less importance in the development of symptoms and signs than the reaction of the individual cardiovascular system to the abnormal load imposed upon it. It will be seen from clinical results which have been reported with Graham (1954), that although symptoms and signs tend to increase in severity with higher diastolic pressures, many patients are encountered with high levels of diastolic pressure who have a minimum of incapacity due to this. This study has shown that approximately 70% of males and 80% of females with hypertension present with breathlessness on exertion and ready fatigue as their symptoms, and a comparable incidence has been found of cardiac enlargement. The load of essential hypertension therefore,

produces heart failure. In a proportion of patients, cerebral vascular degeneration takes place with death due to cerebral vascular accident, and others die from renal failure. However these conditions can only be treated by palliative measures and it is congestive heart failure which is the manifestation of hypertension in the early stages.

Hypertension other than essential was rarely encountered, although a careful search was made for causes such as those detailed previously, during the four year period of observation at Paisley. However a further group of patients fell into the category of malignant hypertension in that they were found to have the characteristic retinopathy described by Keith and Wagener (1928). This group may be divided into those in malignant state supervening upon hypertension of long duration, and a group where the rise in blood pressure was of short duration. Their response to treatment will be classified and described subsequently and they form the subject of a special study.

Treatment of Hypertension

Despite the advances in our knowledge which have increased greatly in recent years, no progress has been made in determining a specific factor responsible for the development of hypertension. It is difficult to decide upon a therapeutic course which will avoid the dangers involved in regarding diastolic hypertension as a benign disease, yet

which will not ignore the high morbidity and mortality which it produces. On the one hand it is unjustifiable to investigate too thoroughly and to observe too closely individuals who present with small elevations in the diastolic blood pressure above normal, and on the other it is difficult to ignore accidental findings of high elevations in the diastolic pressure even in the absence of signs and symptoms. In the present study, it was decided to treat patients with hypertension only when signs and symptoms were found, except in a comparatively few instances where the diastolic pressure was very high.

Prior to the introduction of ganglion blocking agents, sympathectomy was the recognised method of treatment of patients with severe signs and symptoms of hypertension. In this operative treatment of hypertension bilateral splanchnic nervic resection has been developed to the point where the sympathetic control of a major portion of the arterioles has been interrupted. The main exponent of this technique has been Smithwick who from 1934 onwards has performed his operation upon several hundred patients. Less extensive procedures have been adopted by Peet et al (1940) and Adson et al (1940). The trend at present in America is to employ a total or subtotal adrenalectomy combined with a modified sympathectomy. Jeffers et al (1953) have examined the results for the treatment of this type, finding an

excellent response in 23%, a fair response in a further 23%, but poor responses were obtained in 30%, and 24% died post-operatively. The American viewpoint upon the indications for adrenalectomy is becoming more conservative, and Bowers (1954) has suggested that this operation should be restricted to malignant hypertension which cannot be controlled by medical therapy, chronic hypertension with marked organic changes, and Cushing's syndrome. With increasing experience it is to be expected that the present measures of treatment with the drugs becoming available, will completely supercede surgical measures.

Now that effective drugs are available which will lower the blood pressure, centres which are engaged upon the study of the methods of treatment of hypertension are tending to become preoccupied with experience in effecting treatment by hypotensive measures such as the study recorded by Smirk (1954). Prior to the introduction of these drugs, methods were available which have not lost their value. The tenets of Fishberg (1936) are still valid, and cannot be modified despite the volume of research and experience which has accumulated since then. It is essential to treat hypertension by relief of environmental stress, employing sedation for this purpose as required. Dietary treatment is still advisable, and certainly hypertension and obesity form a common combination. An exaggerated regime such as the

Kempner (1948) diet owes part of its value only to psychological influences. As Schroder et al (1939) have pointed out, this diet represents a low calorie intake, it is low in protein content and very low in salt. Fishberg has shown that it is essential to reduce the calorie intake in the treatment of hypertensive heart failure as a heavy meal increases the load upon the heart to an extent comparable with physical exertion. Dietary limitation should be practised even in the absence of seeking weight loss, as it is followed by a reduction in the basal metabolic rate, thereby decreasing the load upon the heart. It is probable that this ready method of therapy is in part responsible for the better prognosis of patients with hypertension who have obesity compared with those of normal weight.

In many cases congestive heart failure occurs. Despite the introduction of the hypotensive drugs, orthodox methods of treatment are indicated. With left ventricular failure, the blood pressure falls and an early sign is found, a falling pulse pressure. The application of hypotensive measures is probably contraindicated in congestive failure with a low pulse pressure. If these drugs are given to patients in failure with low pulse pressures, there is a tendency for a further reduction, increasing the venous congestion.

THE DRUG TREATMENT OF HYPERTENSION

A number of drugs are in use at present for the treatment of hypertension. These are all claimed to have some action in reducing the blood pressure, and the indications for their use in addition to general measures of treatment and their relative value have been summarised by Graham and myself (1954).

For convenience they may be divided into two main groups, synthetic and alkaloid. The value of each of these drugs remains to be defined. Their main characteristics are presented in the following table.

SYNTHETIC

	: Site of action	: Trade name
Hexamethonium	: ganglion blocking agents	: Hexathide
Methonium homologues	:	: Vegolysen
Pentapyrrolidinium	:	: Ansolysen
Hydrallazine (1-hydrazinophthalazine)	: central depressant : peripheral vasodilator : antagonist to: angiotonin: : serotonin: : pherentasin:	: Apresoline

ALKALOID

	site of action	Trade name
Reserpine (Rauwolfia serpentina)	central depressant	Serpasil (pure alkaloid) Rauwiloid (crude extract)
Veratrum viride	central depressant and peripheral vagal stimulant	Veriloid
Hydrogenated alkaloids of ergot: Dihydroergocornine Dihydroergocristine Dihydroergokryptine	central depressant, and peripheral adrenergic blocking actions.	Hydergine

SYNTHETIC DRUGS

Ganglion Blocking Agents: Hexamethonium

The circumstances leading to the discovery of hexamethonium have been reviewed, together with the application of this drug in the treatment of hypertension. The literature is now extensive and the relevant references are appended in the bibliography. The advantages and disadvantages of this drug can be summarised as follows:-

a) Advantages In at least 80% of patients with hypertension, hexamethonium by parenteral dosage will produce a fall in the blood pressure, which apart from individual degrees of sensitivity to the first dose, is largely determined by the quantity of drug injected. The fall in the blood pressure is

greater than can be produced by any other drug or measure, other than extensive sympathectomy or adrenalectomy. It may be used readily, as compared to operative treatment which it has almost completely superceded. Even in full dosage the side actions are limited in extent.

b) Disadvantages. Tolerance to hexamethonium develops very rapidly. Continuous parenteral injections only are effective in the treatment of some patients. The high activity restricts its application to patients with severe hypertension. Oral absorption is unpredictable and irregular. During drug action postural hypotension may be severe and occasion sudden loss of consciousness. Side actions, such as mydriasis and cycloplegia, are not usually troublesome, but dryness of the mouth may occasionally necessitate withdrawal of dosage. Ileus is an ever present risk during sustained and particularly oral dosage. While excellent results may be obtained with in-patient treatment with hexamethonium, return to activity is followed by a rise in the blood pressure despite continuous hexamethonium dosage and further admissions to hospital may be desirable. Both during initial dosage and during maintenance of treatment, skill is required in the supervision of patients. The drug is unsuitable for patients at home, except under very favourable circumstances, and it is too active for the treatment of patients with mild or moderate degrees of hypertension.

However, the excellent results which can be obtained with active drugs of this type are evidenced in the review by Smirk (1954) which shows the necessity for a specialised interest in the treatment of this disease.

Methonium Homologues

Methonium homologues offer possibilities of more satisfactory treatment. As a result of this study, pentapyrrolidinium is now available as a hypotensive drug with a high degree of activity.

Hydrallazine. In 1950 Gross et al described the actions of a number of compounds of the phthalazine series which they found produced a slow depression of the blood pressure of long duration, together with an increase in renal blood flow, and they had antiadrenergic activity. Of these 1-hydrazinophthalazine was the most active. The activity and toxicity of 1-hydrazinophthalazine was studied in animals by Craver et al (1951) and Walker et al (1951). Freis and Finnerty (1950) demonstrated that this drug antagonised the pressor response to adrenalin and showed relatively little activity against noradrenalin. They studied the hypotensive action in normotensive and hypertensive patients. Clinical investigations were conducted by Page (1951), Schroeder (1952), Taylor et al (1952), and others. Combined therapy with hexamethonium has been practised using hexamethonium to produce a marked fall in the blood pressure and 1-hydrazinophthalazine to sustain the effect and regularise the variations

in pressure which occur during methonium treatment. The combined action of these drugs is not without dangers, and Grimson et al (1952) advised caution in their administration, recommending hospitalisation during induction of treatment.

During investigation in this hospital, little place was found for 1-hydrazino-phthalazine in treatment. The side actions in the form of headache, nausea, and tachycardia proved troublesome, and no significant advantage was found in combining 1-hydrazino-phthalazine with hexamethonium as it produced little effect upon the blood pressure, and newer compounds of the ganglion blocking series were available. Smirk has been in agreement with these findings.

ALKALOIDS

Reserpine. A shrub with long snake-like roots growing in India and South East Asia named *Rauwolfia serpentina* was reputed to have a medicinal value. Systematic study of this plant commenced in 1931 when crystalline substances were extracted from its roots, and in 1942 Bhatia reported favourable results in the treatment of hypertension, a more extensive study being made by Vakil (1949). A pure alkaloid named Reserpine was extracted by Muller et al (1952). There have been many observations upon the effects of extracts of *Rauwolfia* in the treatment of hypertension, such as those of Wilkins (1953), Doyle and Smirk (1954), and Joiner and Kauntze (1954). This drug is supposed to act by depressing the blood

pressure regulating centres in the hypothalamus, and is said to produce a fall in blood pressure to a useful extent in 50% of patients treated. The main side action is bradycardia, but Doyle and Smirk have noted flushing, nasal congestion, vertigo, vomiting and diarrhoea during heavy dosage. The euphoric action of this drug has been employed in the treatment of patients with mental disease. Doyle and Smirk have combined Reserpine with pentapyrrolidinium in the treatment of hypertension with promising results.

In view of the history of the development of Reserpine and its unsatisfactory pharmacological state of investigation, this drug was applied with caution in the treatment of a number of patients, and the results, despite investigation which lacked optimism, appeared to indicate a possible usefulness for Reserpine in the management of patients with the less severe grades of hypertension.

Veratrum Alkaloids The actions of Veratrine, alkaloidal extracts of Green Hellbore, have been subjected to a pharmacological study of some duration. In 1949 Stutzman et al prepared alkaloid extracts of hypotensive activity, reporting the findings in greater detail in 1951. The final extract they named Veriloid. This alkaloid produces a depression of the blood pressure by a central depressant action upon the hypothalamus, and by stimulating the vagal peripheral sensory receptors, thus through a reflex arc producing bradycardia and peripheral vasodilation. It has no adrenergic blocking

properties. The main side action is irritation of the gastric vagus with the production of nausea and vomiting. It has been used extensively in the treatment of hypertension, its effects having been noted by Kauntze and Trounce (1951), Wilkins et al (1949), and others. Recently it has been used in combination with Reserpine by Joiner and Kauntze (1954). During investigation of this drug personally, it was found that a marked hypotensive action could be obtained in some patients, but in the majority the effect upon the blood pressure was limited by profound nausea and occasional vomiting.

Hydrogenated Alkaloids of Ergot. The alkaloids of ergot are known for their constrictor action on smooth muscle, and their production of vasoconstriction. They have a weak sympatholytic action which is obscured by their main activities. In 1949 Rothlin and Cerletti demonstrated that the hydrogenated alkaloids were capable of obstructing the vasoconstrictor actions of the parent alkaloids. A mixture of the three hydrogenated alkaloids or ergot, D.H.O.180, D.C.S.90, and D.H.K.135, have been employed in the treatment of hypertension as the preparation hydergine (C.C.K.179). The actions of these alkaloids in man have been studied extensively by Goetz (1949 and 1951), Goetz and Katz (1949), Hafkenschiel et al (1950), and others. Hydergine produces a fall in the blood pressure by a central depressant action, but its main activity is the production of vasodilation. Experience of

this drug indicated that the fall in blood pressure was seldom adequate for the treatment of severe hypertension. Nausea and headache were found to be troublesome side actions.

Dibenamine This drug and its analogues, by adrenergic inhibition, may cause a fall in the blood pressure, but their use is limited to a possible value in the diagnosis of phaeochromocytoma.

CLINICAL TRIAL OF PENTAPYRROLIDINIUM

Pentapyrrolidinium was applied in the treatment of three groups of patients.

1. Patients under treatment with hexamethonium.

Sixty-two patients were selected. These patients were suffering from severe hypertension and their investigation and treatment were described previously with Graham and Campbell (1952). During outpatient management their pressure levels had risen despite parenteral and oral hexamethonium, with recurrence of symptoms and signs. In every case parenteral pentapyrrolidinium dosage reaching a maximum of between 100 - 200 mg. per day controlled their blood pressure levels. It was found that a suitable test dose was 5 mg. of cation subcutaneously, and following this, continuous dosage was employed commencing with 10 mg. morning and night. The majority of patients responded well to dosage of 40 mg. twice daily. In accordance with the experience of Smirk (1954), a single morning dose of 40 - 100 mg. of pentapyrrolidinium in polyvinylpyrrolidone was often found sufficient. Oral dosage was found to be practical in twenty-six of these patients, and consisted of initially 40 mg. tablets in dosage rising to one, four times a day. Eleven patients required treatment with 200 mg. tablets, a maximum dose of one, four times a day being required. In common with the experience with hexamethonium, tolerance was found to develop over a period of six

weeks to three months, but control of pressure levels was still possible by withdrawing dosage for a period of three months or more and then beginning again, in some cases alternating treatment with hexamethonium, cross tolerance being negligible.

The depression of the blood pressure obtained with pentapyrrolidinium was much more stable than that obtained with hexamethonium, and marked elevations of pressure in response to emotion did not occur. The duration of individual doses was longer, varying between four and twelve hours. Side actions were experienced. Dryness of the mouth was seldom troublesome, but mydriasis was found in fifty-seven of these patients, and in seventeen this was accompanied by cycloplegia. An unusual feature was occurrence of diarrhoea which necessitated withdrawal of this drug in seventeen of the patients treated. Fourteen patients complained of mental depression.

The results are in agreement with those described by Smirk (1954) who regards pentapyrrolidinium as a definite improvement over hexamethonium in the management of hypertensive cases.

2. Hypertension treated with pentapyrrolidinium.

Twenty-three patients with hypertension with severe signs and symptoms were treated with pentapyrrolidinium from the first admission. The duration of treatment varied between four and eighteen months. Pentapyrrolidinium was found to be active and safer to use. Overdosage produced less risk

to life than in the case of hexamethonium. e.g.

A male patient age 51 years, was admitted in early congestive failure with a blood pressure of 260/160 mm. A test dose of 5 mg. of pentapyrrolidinium was prescribed and due to a confusion over the strength of the solution, 50 mg. was given intramuscularly. This represented an equivalent of between 250 - 500 mg. of hexamethonium - approaching 500 - 1,000 mg. of the bromide salt. The patient was kept recumbent. His blood pressure fell to 130/90 and did not commence rising until 36 hours later, reaching 230/130 60 hours after the drug dosage. At no time were hypotensive symptoms experienced, cardiac embarrassment was not apparent, and there was no interference with fluid output. Noradrenalin was available as an antidote, but there was no indication for its administration.

To a less extent this experience applied in the treatment of patients generally. Overdosage was shown by the production of vertigo, and the patients themselves during outpatient observation were often able to adjust their dosage to below the threshold of production of this hypotensive symptom with safety, in contrast to the sudden loss of consciousness experienced during full dosage of hexamethonium. Side actions were those described above.

3. Malignant hypertension

Nine of the patients recorded with malignant hypertension

were treated with pentapyrrolidinium. A much more satisfactory control of their blood pressure levels was obtained than with hexamethonium, particularly in the cases of the patients with primary malignant hypertension. However those with chronic malignant hypertension developed tolerance during the longer administration of this drug.

Phenyldimethonium was applied in the treatment of twenty-one patients, some of whom had been treated previously with hexamethonium, pentapyrrolidinium, or both. Its action in depressing the blood pressure was less consistent than that of pentapyrrolidinium, but side effects were less and were composed almost entirely of mydriasis. Phenyldimethonium appears to occupy a position intermediate between hexamethonium and pentapyrrolidinium, and although it was found useful in enabling a further variation of the hypotensive agent employed, frequent use was not indicated.

MALIGNANT HYPERTENSION

Hypertension of the malignant type is uncommon. It is characterised by the appearance of papilloedema, which differentiates it from hypertension in benign form and is an ominous prognostic sign.

In 1926 Keith and Wagener presented studies upon the fundal changes of a number of patients with severe hypertension to the American Ophthalmic Association, and in 1928 they defined malignant hypertension as characterised by severe hypertension and fundal changes in the form of haemorrhages, exudates, alterations in the appearance in the retinal arteries, and essentially papilloedema. Despite the early recognition of the malignant phase of hypertension by Janeway in 1913, and Volhard and Fahr in 1915, the study by Keith and Wagener produced the first recognition of the association of papilloedema with rapidly fatal hypertensive disease.

Despite its relatively infrequent occurrence, malignant hypertension has attracted attention because progress is often rapid, changes taking place in weeks or months which may occur in a similar number of years in patients with benign hypertension. The vascular response is different in that the rise in pressure is so rapid that arterial fibrosis and arteriolar fibrinoid change is replaced by an acute arteriolitis. Although many patients die from

cerebral vascular catastrophes, not uncommonly the termination is due to renal failure.

Many series of cases have been reported such as those by Ellis (1938), Page (1939) and Schottstaedt and Sokolow (1953); and Wilson (1953) has drawn parallels with the experimental production of hypertension in animals.

In the clinical studies from which data has been accumulated, it has been especially difficult to determine the prognosis in this group of patients. In many, the disease progresses to a fatal termination within a few months. In some young patients apparently having the disease in the acute form, life has extended to several years. A number of patients have had spontaneous remissions with disappearance of papilloedema, and some have enjoyed a normal duration of life.

Owing to the infrequent occurrence of this condition, reports upon the response to treatment with ganglion blocking agents have been few and upon isolated cases, and it has not been possible to draw any conclusions from them. During the last four years, sixteen patients have been treated at Paisley with methonium compounds. This number has been just sufficient to afford an analysis of the response to treatment, and to suggest sub-division of patients with malignant hypertension into two main groups, the first of which may again be divided.

In eight of the patients the malignant hypertension followed hypertension of many years duration as evidenced by

history and observation at home, and during hospital investigation. These patients tended to be of a rather older age group whose ages ranged from 39 - 59 years. The heart was found to be enlarged clinically and radiologically in response to the load imposed by chronic hypertension, electrocardiographic changes evidenced left ventricular strain and hypertrophy. Vascular changes of sclerotic type were present, renal function was good and albuminuria infrequent. The fundi showed retinal arteriosclerosis and a late picture of waxy hyaline exudates with chronic papilloedema. Fresh haemorrhages and woolly exudates were observed at some point during the course of the disease and tended to resolve during treatment. Papilloedema regressed during treatment also, but optic atrophy tended to be progressive. These patients generally presented with signs and symptoms due to cardiac failure. Their response to treatment with hypertensive drugs was good and the prognosis extended to four years or more. Five presented difficulties in outpatient management. When they returned to work it was found to be impossible to control adequately their pressure levels as outpatients. Two patients in this group have died. In the first, a woman of 44 years, cerebral vascular changes had been responsible for mental deterioration prior to admission to hospital. When admitted with heart failure a good response was obtained to dosage of pentapyrrolidinium, with decrease in heart size and marked

improvement in electrocardiographic changes. However she insisted upon returning home and discontinuing treatment, and died three months after irregular discharge. Renal failure occurred in the second case, a male of 59 years, the disease assuming a fulminating form and failing to respond to treatment.

To this group the term "malignant phase" has been applied in that these patients have had hypertension for several years and their pressure has risen slowly to unsupportable levels. The cardiovascular system has been reinforced and renal insufficiency is an uncommon form of death. Treatment of this group by general measures of rest and sedation, together with, if possible, some reduction in the pressure level by hypertensive drugs was followed by an indeterminate period of life expectation.

In the second group in which the patients were generally rather younger, severe hypertension was of recent onset. No evidence of arteriosclerosis was present and cardiac enlargement was not demonstrable during initial examination, but occurred in some cases after several months. The fundi showed fresh haemorrhages and woolly exudates with papilloedema. This group included patients with a history, renal changes suggestive of, and post-mortem findings confirming, glomerulo-nephritis. Four patients had no history of renal disease, showed no evidence of renal impairment, and were found

to have post mortem changes consistent with a diagnosis of malignant hypertension. All the eight patients in this group died in uraemia with a marked hypochromic anaemia. Their response to treatment confirmed the indication for subdividing this group into those patients who had renal disease and those who may be considered to have had a primary malignant hypertension. Of those with hypertension of renal origin, one died in uraemia within twelve days of observation, no treatment other than palliative being possible. He has been included as a renal case but differentiation from primary malignant hypertension is not possible. Of the other three, use of hexamethonium or pentapyrrolidinium with restoration of low levels of pressure has possibly extended the prognosis to living four years and three years, the third being still alive at three years. Progressive renal failure occurred slowly with a rising blood urea. The response of the patients with primary malignant hypertension was particularly disappointing as this group presented with gross visual impairment. Complete symptomatic relief followed restoration of the blood pressure in all cases to normal levels by intensive application of ganglion blocking drugs. However despite control of the blood pressure, renal failure was progressive and an extension to the life expectation was dubious.

Study of the previous series of cases which have been published suggest a confirmation of the value of this classification in determining the prognosis. The small group of patients with primary malignant hypertension is comparable with certain patients which have been encountered by Smithwick (1948) and others, in whom vascular degeneration and renal failure has progressed despite operative treatment.

MECHANISMS INVOLVED IN THE PRODUCTION OF PEPTIC ULCERATION

There are a number of mechanisms concerned in the stimulation and inhibition of gastric secretomotor activity. Local reflexes and humeral secretions are involved, and the parasympathetic nervous system provides motor impulses. It is recognised that duodenal ulceration is associated with hyperchlorhydria during the interdigestive phase of secretion, due to excessive vagal tone.

A cortical centre for gastric function has not been localised, although Wolf and Wolff (1942) have clearly demonstrated that emotional disturbance is followed by gastric overactivity. Illingworth (1953) has recognised a hypothalamic centre. Further relay stations exist in the medullary nuclei and from these secretomotor impulses are distributed by the vagal nerves. The response of this mechanism was first implicated by Pavlov and Schumova-Simenowskaja (1899) who demonstrated the gastric secretory response to food could be modified by vagotomy. Gastric delay in emptying and dilatation following vagotomy in animals were first described by Starck (1904), and Beal and Dineen (1950) have demonstrated similar findings in man. A depression of secretion also was demonstrated by Shay et al (1947). Woodward et al (1949) have confirmed that very complete surgical division of the vagus is necessary to produce inhibition of gastric activity, and Jefferson et al (1950) have indicated that the posterior

nerve in the dog carries the secretomotor fibres. Experimental division of the vagus is followed after a variable period of time by recovery of gastric function, as has been shown by Machella and Lorber (1948), who suggested the development of other pathways or mechanisms. The action of histamine is peripheral to that of the vagus, and as Beaver and Mann (1931) have shown, a Mann-Williamson (1923) ulceration can still be produced after vagotomy, although Lillehei et al (1950) found a modified response to histamine following vagotomy.

The hypothesis at present accepted suggests that gastric secretion is invoked initially by the upper centre stimulation, continued by local stimulation by the food ingested, and terminated by a humeral mechanism such as enterogastrone. The central stimulation is provided by a reflex arc initiated by sight, smell and taste, together with psychic factors. Dragstedt et al (1949) demonstrated that a high interdigestive secretion is consistently found in patients with duodenal ulceration. The local mechanisms are not of importance in the development of duodenal ulceration in that the acid secretion is adsorbed by the ingested food which provokes it. On the other hand, hyperacidity during interdigestive phase exposes the mucosa to a high concentration of pepsin and hydrochloric acid with opportunity for ulceration. Levin et al (1948) have provided findings in support of this hypothesis

in that their patients who suffered from duodenal ulceration secreted a gastric juice of the volume twice the amount found in normal patients, and of peptic activity three and a half times greater; and further, while the secretion of hydrochloric acid by normal patients tended to be intermittent and variable, consistent high levels were found in those with ulceration. There has been further confirmation by Woodward et al (1949) who found during examination of a large series of duodenal ulcer patients, a quantity of acid secretion three times that in normal subjects.

A definite decrease in the volume of gastric secretion and acidity have been described by Ruffin et al (1946), and Walters and Belding (1951), after vagotomy. The extent to which the vagus can be implicated has not been defined, Grossman (1949) has shown that patients with hyperchlorhydria produced excessive responses to stimuli such as histamine and foods, but such responses would be facilitated by excessive vagal tone.

Although vagal section has been practised from an early date, it was not until 1943 that a systematic investigation of this operation as a method of treatment of peptic ulceration was performed by Dragstedt and Owens. Variable results followed operation, possibly due to the difficulties involved in completely sectioning the vagus. Methods of assessment of the results obtained have not been standardised as has been pointed out by Trimble and Lynne (1950). The results obtained

have been complicated by excessive denervation affecting other organs, and Dailey et al (1952) have suggested section of the posterior nerve only, while Jackson (1948) and Franksson (1948) have practised selective vagal section to relieve the fibres supplying the stomach only, in an attempt to avoid the 10-15% incidence of post-operative symptoms described by White (1948). As Illingworth has indicated, vagotomy is assuming a place in the surgical treatment of peptic ulceration, possibly in combination with other operations upon the stomach.

In 1947 Holt et al demonstrated the action of tetraethylammonium upon the stomach. It was found to diminish the tone and abolish peristaltic activity, reproducing closely the effect of vagal section, and Lyons et al (1947) found it produced a marked reduction in the volume and acidity of acid secretion. Later Macdonald and Smith (1949) confirmed its action in reducing spontaneous gastric secretion. The possibility of producing a vagotomy by drug dosage was attractive, but tetraethylammonium dosage was followed by metallic taste in the mouth, peripheral paraesthesiae, mydriasis and cycloplegia, fatigue and marked hypotension. In turn, hexamethonium was welcomed by Kay and Smith in 1950, who found it capable of arresting spontaneous gastric secretomotor activity, but Douthwaite and Thorne (1950) showed that this could not be accomplished without a risk of severe

hypotension. However Scott et al (1950) were able to use hexamethonium in the treatment of patients with severe chronic duodenal ulceration, producing some improvement in their condition. Hexamethonium is capable of effecting the gastric secretion by parenteral and oral dosage, but unfortunately, in the maintenance of patients with peptic ulceration for long periods with oral dosage, tolerance rapidly develops, there is a risk of hypotension with the dangers which may follow sudden loss of consciousness, and ileus also constitutes a potential risk. Grimson (personal communication) abandoned his clinical trial of hexamethonium in peptic ulceration despite moderately successful results when one of his patients collapsed due to postural hypotension and fractured his skull fatally. However, in the development of methods of production of vagotomy by drugs, hexamethonium must be regarded as an advance of major significance but of experimental rather than practical interest. A homologue such as ethyltetramethonium, with a preponderance of action in depressing vagal activity leaving sympathetic conduction relatively unaffected in the dosage used, is of greater interest in the practical management of patients who have a high interdigestive acid level associated with peptic ulceration, and ethyltetramethonium has therefore been applied in the treatment of these patients.

THE DRUG TREATMENT OF HYPERCHLORHYDRIA

In contrast to the numerous sites of action of the new drugs used to lower the blood pressure, the new synthetic drugs which have been described in America are all atropine substitutes. Their site of action is at the peripheral parasympathetic synapse, with, in common with atropine, some action at the ganglia. They differ in their degree of activity, and in the extent of the side actions they produce, which are identical with those produced by atropine.

Drug	Formula	Trade name
Dibutoline	Dibutylurethane of dimethyl-ethyl-B hydroxyethyl ammonium sulphate	Dibutoline
Methantheline	Ethyl dimethyl B-(9-xanthene carboxylate) ethylammonium chloride	Banthine
S C 3171	B diisopropylaminoethyl xanthene-9-carboxylate methobromide	Pro-Banthine
Prantal	N,N-dimethyl-4-piperidylidene-1,1-diphenylmethane methyl sulphate	Prantal
Darstine	5-methyl-4-phenyl-1-(1 piperidyl)-3-hexanol methobromide	Darstine
A Y 5212	8-diethylaminoethyl phenothiazine-10-carboxylate methosulphate	

Drug	Formula	Trade name
U - 0382	Epoxytropine tropate methylbromode	Pamine
Oxyphenonium	Diethyl(2-hydroxyethyl) methyl: ammonium bromide -phenyl- cyclohexaneglycolate	Antrenyl
Tricyclamol	1-cyclohexyl-1-phenyl-3- pyrrolidino-1-propanol methochloride	Elorine

The bibliography upon these drugs is extensive, the key articles have been noted in the references appended.

The preponderance of compounds of quaternary ammonium termination is evident, with an aromatic opposing termination of variable complexity.

CLINICAL TRIAL OF ETHYLTETRAMETHONIUM

The examination of this drug clinically presented difficulties. It was arranged in three parts:-

1. Study of the effect of repeated dosage.

Fifteen patients with active duodenal ulceration were admitted for investigation. The minimal dose orally active of cation was previously determined as 100 mg. These patients were treated with tablets containing this quantity of cation administered four times in a day, and their interdigestive secretion was investigated at three day intervals, observing precautions previously noted. It was found that ethyltetramethonium produced achlorhydria in ten patients on one or more days of investigation during the first fortnight of dosage, while during the next fortnight of observation, acid levels were lower than in the fortnight prior to admission, but two only reached achlorhydria. Five patients showed low acid levels during drug dosage not to the point of achlorhydria, but half to one fifth of their previous levels, and in three cases this reduction in acidity lasted through the month of observation.

Some delay in emptying of the stomach occurred during barium examination of three patients, but a radiological investigation on a larger scale was not practical. Gastric motility studies were performed upon ten of these patients, but the results proved difficult to interpret, and it was

decided that more extensive experience of this technique would be required before the results would be of value.

During the first three days of treatment, four patients complained of light headedness and showed postural falls of the diastolic blood pressure of the order of 10-20 mm. No further hypotensive symptoms occurred. Mydriasis without cycloplegia was observed in nine patients, appearing on the second day of treatment, and in a further one case this was accompanied by cycloplegia which persisted during drug dosage. Mild dryness of the mouth occurred in four patients, but to an extent insufficient to cause complaint. No gastrointestinal upset appeared, and at no time were laxatives required for constipation. No other side actions were detected.

In view of the potential usefulness of hexapyrrolidinium, ten patients were then treated with this drug in oral dosage of 40 mg. cation four times per day. Postural hypotension developed in four patients three to four days after commencing treatment. Mydriasis was observed in nine, with cycloplegia in three. At the end of the sixth day of treatment, eight patients were found to be drowsy and complaining of headaches and depression. No further dosage of this drug was employed despite the occurrence of achlorhydria in five of the patients.

2. Treatment of In-patients

In view of the results obtained above, ethyltetramethonium

was prescribed for a period in addition to the dietary regime in the treatment of patients admitted with duodenal ulceration, using this drug as a substitute for atropine. The effect upon the symptoms of thirty patients was studied. The results indicated an absence of correlation between an action upon gastric acidity and relief of symptoms, and no deduction could be drawn from the response to ethyltetramethonium and to the control tablets of similar appearance and taste.

Patients admitted to hospital with duodenal ulceration proved to be entirely unsuitable material for the study of the action of new drugs such as this. Upon analysis, it was found that twenty-two of these patients had long histories of duodenal ulceration with perforations and haematemeses. Radiography showed extensive duodenal deformities and deep penetrating ulceration. A further five had recent haematemeses, the effect of which was found to be an initial depression followed by a slow rise in acid level. Three were transferred from surgical wards for medical treatment prior to operation.

It was concluded that patients admitted to medical wards are often unsuitable for medical treatment, the admission being determined by a need for observation prior to gastrectomy. It is unlikely that any medical treatment will be of value in the presence of gross chronic ulceration. Scott et al (1950) have already reached this conclusion. Eight of the thirty patients

obtained relief of symptoms following ethyltetramethonium dosage, and this correlated with a reduction in acidity in seven. The interdigestive acid level was reduced in a further nine patients, but it was not possible to decide whether this had any effect upon the patient's condition.

3. Treatment of Out-patients

In the presence of advanced pathological changes, there can be no doubt that the only satisfactory method of treatment is gastrectomy. However, surgical treatment is indicated only in a small percentage of cases, and the vast majority of patients present with exacerbations and remissions with varying degrees of incapacity. The psychological effect of a new method of treatment is pronounced. Sedation and regular and frequent ingestion of food of a non-stimulating nature to neutralise acid secretion by absorption, together with intermittent dosage of alkalies, are the methods of treatment accepted at present. Unfortunately these measures are often insufficient to control the symptoms of a large number of individuals, and it is probable that many of the failures of treatment are due to insufficient supervision due to the numbers involved, and neglect of dietary precautions. There is every indication for a simply administered treatment which would modify the exacerbations as they occur. For this purpose ethyltetramethonium appeared to be of potential usefulness. It was decided to observe its action

in modifying the interdigestive secretion with the relief of symptoms upon a moderately large series of outpatients, using a control by provision of inert tablets. The position is different from that occurring in the treatment of hypertension in which continuous control of the blood pressure level is desirable so that there is a major difficulty in the form of the development of tolerance to the drugs used. In the case of duodenal ulceration, intermittent dosage is practical in that exacerbations tend to occur at intervals of several months. Accordingly, it was decided to use ethyltetramethonium for courses of treatment which would not exceed four weeks in duration, as it had been found previously that tolerance did not tend to develop to the extent of vitiating the drug action for at least three weeks. Two schemes of dosage were employed, the first for patients with more severe symptoms. One tablet was given twice a day for the first three days, and subsequently four tablets were given per day, the course lasting ten days to three weeks, aiming usually at commencing treatment whenever symptoms were complained of, and continuing treatment for one week after relief of symptoms had been obtained. The second method of treatment consisted of the prescription of three tablets at night to depress the nocturnal secretion.

It was necessary to avoid any suggestion to the patients that a new drug was being used, and also to avoid their

segregation at a special hour and clinic. They were seen at outpatient dispensaries and in outpatient attendance at the wards. Alternate patients were treated with the control tablets initially. A total of one hundred patients were observed for eighteen months for the preparation of this study. Sedation was continued, together with intermittent alkali dosage, where these methods of treatment were already being used. Administration of atropine was discontinued. The patients had a history of one to twenty-seven years duration, their ages were between 17-54 years. Ninety-four were males and had radiographic evidence of duodenal ulceration. The results are summarised in the following tables:-

Group I - 50 patients

	Work lost days.	Number of exacerbations	Duration of symptoms weeks.
Treatment 9 months	2.7	2.1	3.7
Control 9 months	3.2	2.5	6.4

Group II - 50 patients

	Work lost days.	Number of exacerbations	Duration of symptoms weeks
Control 9 months	11	3.5	8.2
Treatment 9 months	1.8	2.5	3.4

The first group were treated with control tablets identical in size and taste with ethyltetramethonium, for the first nine months. The procedure was reversed in the second group.

It appears that ethyltetramethonium has been useful in reducing the duration of invalidism to a definite extent. The results are very suggestive of the value of ethyltetramethonium in the outpatient treatment of duodenal ulceration, but in view of the many factors which influence the course and prognosis in this disease, they can be accepted as tending only to confirm the experimental findings, and the practical value of this drug will be determined only by a much more extensive clinical trial with scrupulous control. In the meantime, its use as a substitute for atropine with orthodox methods of treatment appears to be indicated, and its eventual value will be determined when quantities of the drug become available for clinical use. No side actions were observed during this trial, but an 8% incidence of mydriasis was noted, without cycloplegia.

CONCLUSION

This study of homologues of the methonium series has followed principles which are being used extensively in extending knowledge of physiological mechanisms. Hexamethonium is being used upon an increasing scale to investigate autonomic nervous activity, and the new compounds described in this work are of interest in that by modifying the structure of hexamethonium, it is possible to alter the predominant site of action in the autonomic nervous distribution. Processes of modification such as these are being used to either reproduce or to obstruct the activity of a wide range of drugs. It is of interest to compare the reversal of action obtained by hydrogenation of the alkaloids of ergot, and the studies of Gaddum et al (1953) and others, of modifications in the form of lysergic acid diethylamide, which together with the investigation of Shaw and Woolley (1953) of harmine and yohimbine, are based upon the indole nucleus with a substituted aminoethyl side chain having a resemblance to serotonin.

In the case of the methonium homologues, the alterations to the molecular structure which have been made, together with the determination of differences in activity, enable advancement of a hypothesis that for different distributions of autonomic nervous function, there may exist different types of synapse; which would suggest that acetylcholine may

be a master key to the synapse, rather than a universal physiological chemical transmitter, reverting thus to the original views of Dale in 1915, partly substantiated by the studies of Burgen (1954). Further, the high activity of drugs such as the pyrrolidines and morpholines, suggests that the affinity for the receptor is physical rather than chemical; a study of the sulphur homologues may support this suggestion. The preparation of compounds based upon a known active structure is useful in that, as well as extending the knowledge of drug action, new drugs may be discovered which as well as having slight differences in action, will be of value in having a greater degree of activity and duration of action due to their differences from the parent compounds.

The production of new compounds of therapeutic value was aimed at in this work with the discovery of pentapyrrolidinium and ethyltetramethonium.

Pentapyrrolidinium

As Smirk (1954) has confirmed, pentapyrrolidinium is the most active drug known in lowering the blood pressure. Its importance is, of course, limited by the fact it represents symptomatic treatment of a disease of which the aetiology is unknown. Page (1953) has shown that hypophysectomy is the only method of control of experimental hypertension; pentapyrrolidinium will lower the blood pressure of any patient with hypertension. Of the many factors involved in the aetiology of hypertension

in man, the actual production of the hypertension is a function of the sympathetic nervous system. A small number of patients were discovered during this work who have been classified as suffering from malignant hypertension in primary form. Despite the restoration of normal blood pressures in these individuals, little if any extension in prognosis was obtained, and death ensued from progressive vascular deterioration which could not be attributed during treatment to hypertension. Similar changes have been described following sympathectomy, and it is possible that the search for the aetiology of hypertension may be extended by identification of biochemical changes in this group of patients.

The application of ganglion blocking agents has enabled an assessment of other current methods of therapy to be made. Of the drugs mentioned, the alkaloid reserpine alone appears to hold some promise of future usefulness. Dosage of reserpine may be combined with ganglion blocking agents to permit of the control of the pressure of some patients whose initial response has relapsed following discharge from hospital.

It is to be expected that better ganglion blocking agents will be developed. The further studies by Woolley and Shaw (1954) upon serotonin inhibitors such as Medmain, may result in a new method of therapy. Bain (unpublished)

has been concerned with impairment of amine oxydase as a cause of hypertension. The studies of MacDowall and Soliman (1954) are of immense interest as they indicate that blocking agents act by causing an accumulation of sodium at specific receptors. Therefore, the action of desoxycorticosterone may be more than a crude process of governing sodium excretion; perhaps it is involved in the intimate process of sodium transfer at ganglia, thereby explaining its known activity in the experimental production of hypertension, and the effect following adrenalectomy of restriction of sodium intake.

Ethyltetramethonium

The investigation of drugs of this type is specialised, requires experience and facilities, and must be extensive. This new compound has been investigated to an extent only sufficient to endorse the experimental results. It is possible that it will be of use therapeutically and this will be determined when supplies are available for use at the centres interested.

EXPERIMENTAL RESULTS

A part of the experimental records is summarised herewith to provide an indication of the type of results obtained during this investigation. Further detail is available in the publications.

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug	
		Erect	Recumbent	Erect	Recumbent
15	56	120/80	115/80	---	80/70
18	56	115/80	110/80	100/70	110/70
24	56	110/80	110/80	---	95/70
41	28	110/75	115/80	100/65	110/65
49	56	115/80	110/75	90/75	100/70

Average change in Recumbent diastolic pressure -9

Average change in Erect diastolic pressure Marked postural fall.

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C.			Thermal Circulation Index.	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after.
15	36.4	32.8	29.8	20.0	36.4	33.6	30.3	1.50	1.70
18	36.2	34.8	30.8	20.0	36.2	33.5	34.2	2.10	7.00
24	36.6	33.0	29.0	20.0	36.6	32.6	29.0	1.20	1.20
41	36.8	34.3	30.3	20.0	36.8	34.3	33.0	1.58	3.50
49	36.2	32.3	30.2	20.0	36.2	32.0	32.0	1.70	2.90

Average Umbilical-Foot Temperature Gradient before 3.2°C

Average Umbilical-Foot Temperature Gradient after 1.1°C

Average Reduction in Gradient 2.1°C

Average Thermal Circulation Index before 1.62

Average Thermal Circulation Index after 3.26

Ratio 2.00

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After		Before	After	
15	5	4	-	76	90	+
18	4	8	+	72	88	+
24	4	4	-	88	84	+
41	3	7	+	84	92	+
49	5	7	-	80	92	+

Average pupil size before 4.2 mms.
 Average pupil size after 5.6 mms.
 Average change in pupil size +1.4 mms.

Accommodation paralysis 2

Average pulse rate before 80.0 per minute.
 Average pulse rate after 88.8 per minute.
 Average change in pulse rate +8.8 per minute.

Dry Mouth 0

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
15	40	60	1.50
18	20	100	5.00
24	150	300	2.00
41	45	80	1.66
49	75	250	3.33

Average Ratio 2.70

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug.	
		Erect	Recumbent	Erect	Recumbent
29	13	130/80	135/80	130/80	120/80
31	13	130/80	120/80	---	95/65
38	13	125/85	120/90	---	85/70
40	5	110/70	100/65	85/70	105/70
257	5	110/75	110/70	100/65	105/70

Average change in Recumbent diastolic pressure -8

Average change in Erect diastolic pressure Marked postural fall.

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after.
	29	36.2	33.0		26.4	20.5	36.2	33.5	28.2
31	36.2	33.5	28.2	20.5	36.2	32.5	30.5	0.98	1.80
38	36.8	28.6	28.6	20.5	36.8	32.4	30.4	0.98	1.55
40	36.4	27.2	27.2	20.5	36.4	33.4	28.8	0.72	1.10
257	36.4	29.4	29.4	19.8	36.4	32.2	27.8	1.35	0.92

Average Umbilical-Foot Temperature Gradient before 5.1°C

Average Umbilical-Foot Temperature Gradient after 3.7°C

Average Reduction in Gradient 1.4°C

Average Thermal Circulation Index before 0.93

Average Thermal Circulation Index after 1.27

Ratio 1.37

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After		Before	After	
29	4	6	-	68	80	+
31	4	3	-	60	64	+
38	3	4	-	72	100	+
40	2	2	-	78	68	+
257	3	3	-	88	96	+
Average pupil size before			3.2 mms.			
Average pupil size after			3.6 mms.			
Average change in pupil size			+0.4 mms.			
Accommodation Paralysis			0			
Average pulse rate before			73.2 per minute.			
Average pulse rate after			81.6 per minute.			
Average change in pulse rate			+8.4 per minute.			
Dry Mouth			0			

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
29	95	200	2.10
31	30	75	2.50
38	18	60	3.33
40	50	75	1.50
257	45	75	1.66

Average Ratio 2.22

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug.	
		Erect	Recumbent	Erect	Recumbent
153	15	120/80	120/80	100/80	120/80
154	15	110/80	110/80	110/80	110/80
156	15	110/65	115/70	100/60	110/65
158	15	110/70	115/75	100/70	110/70
161	15	120/80	125/85	100/80	105/80

Average change in Recumbent diastolic pressure -1

Average change in Erect diastolic pressure -1

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after
153	36.4	31.3	28.0	19.8	36.4	34.3	28.2	0.98	1.00
154	36.6	33.3	28.8	19.8	36.6	33.0	28.6	1.18	1.10
156	36.6	32.5	31.0	19.8	36.6	31.5	28.9	2.10	1.20
158	33.8	33.8	28.8	19.8	36.6	33.0	31.0	1.18	2.10
161	35.0	35.0	30.3	19.8	36.8	33.8	27.3	1.58	0.78

Average Umbilical-Foot Temperature Gradient before 3.8°C

Average Umbilical-Foot Temperature Gradient after 4.3°C

Average Increase in Gradient 0.5°C

Average Thermal Circulation Index before 1.42

Average Thermal Circulation Index after 1.24

Ratio 0.87

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After		Before	After	
153	3	3	+	68	72	+
154	3	3	-	80	84	+
156	3	4	-	84	92	+
158	4	3	-	80	68	+
161	3	3	-	72	72	+
Average pupil size before			3.2 mms.			
Average pupil size after			3.2 mms.			
Average change in pupil size			0			
Accommodation Paralysis			0			
Average pulse rate before			76.8 per minute.			
Average pulse rate after			77.6 per minute.			
Average change in pulse rate			+0.8 per minute.			
Dry Mouth			0			

EFFECT UPON THE SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
153	25	45	1.80
154	30	35	1.17
156	40	45	1.13
158	300	400	1.33
161	100	500	5.00

Average Ratio 2.08

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug.	
		Erect	Recumbent	Erect	Recumbent.
150	25	125/80	125/80	105/80	100/80
152	25	140/80	135/80	---	80/60
243	10	125/80	125/80	---	80/60
254	5	100/70	100/70	100/70	100/70
256	10	125/85	125/85	110/80	110/80

Average change in Recumbent diastolic pressure -9

Average change in Erect diastolic pressure Marked postural fall.

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C.			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation. Index.	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after.
	150	36.8	33.8		28.8	19.0	36.8	34.0	32.3
152	37.0	35.0	29.8	19.0	37.0	34.5	32.0	1.50	2.70
263	36.4	34.2	27.6	19.2	36.4	34.0	27.4	0.95	0.93
254	36.8	34.2	27.4	19.8	36.8	34.6	27.6	0.80	0.82
256	36.8	31.8	30.4	19.8	36.8	32.0	29.8	1.70	1.40

Average Thermal Circulation Index before 1.34

Average Thermal Circulation Index after 1.76

Ratio 1.31

Average Umbilical-Foot Gradient before 5.0°C.

Average Umbilical-Foot Temperature Gradient after 4.0°C

Average Reduction in Gradient 1.0°C

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After		Before	After	
150	3	6	+	72	108	+
152	3	6	+	68	96	+
263	3	5	+	72	80	+
254	3	4	-	76	68	+
256	3	5	-	80	72	+
Average pupil size before			3.0 mms.			
Average pupil size after			5.2 mms.			
Average change in pupil size			+2.2 mms.			
Accommodation Paralysis			0			
Average pulse rate before			73.6 per minute.			
Average pulse rate after			84.8 per minute.			
Average change in pulse rate			+11.2 per minute.			
Dry Mouth			0			

EFFECT UPON THE SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after.	
150	35	59	1.43
152	75	90	1.20
263	60	70	1.17
254	18	25	1.37
256	35	95	2.71
Average Ratio		1.54	

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug.	
		Erect	Recumbent	Erect	Recumbent.
63	36	110/80	110/80	110/80	110/80
67	27	120/85	150/90	115/85	120/80
68	21	110/75	100/70	95/70	95/70
74	36	105/85	100/80	95/75	105/80
76	30	130/85	150/90	100/80	120/95

Average change in Recumbent diastolic pressure -1

Average change in Erect diastolic pressure -4

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before.			Room Temp. °C	1 hr. after.			Thermal Circulation Index.	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after.
63	36.8	34.0	31.5	19.0	36.8	33.4	31.5	2.40	2.40
67	37.0	32.0	25.0	19.0	37.0	32.0	22.5	0.50	0.25
68	36.6	32.8	27.0	19.0	36.6	31.6	26.4	0.85	0.74
74	37.0	33.5	28.5	19.0	37.0	32.5	29.5	1.15	1.40
76	36.4	32.5	28.5	19.0	36.4	31.5	27.8	1.20	1.03

Average Umbilical-Foot Temperature Gradient before 4.9°C

Average Umbilical-Foot Temperature Gradient after 4.7°C

Average Reduction in Gradient 0.2°C

Average Thermal Circulation Index before 1.22

Average Thermal Circulation Index after 1.12

Ratio 0.90

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After.		Before	After	
63	5	5	-	88	88	+
67	6	5	-	72	72	+
68	4	4	-	64	64	+
74	4	3	-	84	84	+
76	3	3	-	72	76	+

Average pupil size before
Average pupil size after
Average change in pupil size

4.4mms.
4.0mms.
-0.4 mms.

Accommodation Paralysis

0

Average pulse rate before
Average pulse rate after
Average change in pulse rate

76.0 per minute.
76.8 per minute.
+0.8 per minute.

Dry Mouth

0

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after.	
63	25	50	2.00
67	40	75	3.13
68	100	170	1.70
74	150	200	1.33
76	35	60	1.71

Average Ratio 1.97

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after	
		Erect	Recumbent	Erect	Recumbent
149	12.5	125/90	130/90	105/75	115/80
151	12.5	120/80	120/80	---	85/50
165	12.5	110/70	110/70	---	95/65
166	5	140/90	145/90	---	80/70
172	5	115/70	115/70	100/65	110/65
Average change in Recumbent diastolic pressure				-12	
Average change in Erect diastolic pressure				Marked postural fall.	

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index.	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after
	149	36.2	34.3		27.8	17.5	36.2	34.8	33.8
151	36.4	32.3	29.8	17.5	36.4	31.0	31.0	1.85	2.50
165	36.2	36.2	29.5	17.5	36.2	32.6	31.5	1.80	3.00
166	36.2	31.5	28.3	17.5	36.2	31.5	29.5	1.35	1.80
172	36.4	32.3	28.6	17.5	36.4	32.2	29.2	1.40	1.60
Average Umbilical-Foot Temperature Gradient before							3.8°C		
Average Umbilical-Foot Temperature Gradient after							1.4°C		
Average Reduction in Gradient							2.4°C		
Average Thermal Circulation Index before					1.52				
Average Thermal Circulation Index after					3.18				
Ratio							2.08		

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After		Before	After.	
149	3	8	+	64	96	+
151	3	7	+	68	72	-
165	3	7	+	64	76	+
166	2	5	+	60	84	-
172	3	7	+	72	88	+

Average pupil size before 2.8 mms.
 Average pupil size after 6.8 mms.
 Average change in pupil size +4.0 mms.

Accommodation Paralysis 5

Average pulse rate before 65.6 per minute.
 Average pulse rate after 83.2 per minute.
 Average change in pulse rate +17.6 per minute.

Dry Mouth 2

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
149	300	400	1.33
151	500	450	0.90
165	400	550	1.38
166	20	30	1.50
172	35	50	1.43

Average Ratio 1.31

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after	
		Erect	Recumbent	Erect	Recumbent.
86	5	110/70	110/70	110/70	110/70
97	10	130/85	140/80	115/90	115/90
98	10	135/85	130/90	135/85	140/90
99	10	110/80	110/80	110/80	110/80
100	5	115/85	110/80	125/90	130/90

Average change in Recumbent diastolic pressure +4

Average change in Erect diastolic pressure +2

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after
	86	36.8	34.0		28.8	18.6	36.8	34.5	31.0
97	37.0	33.4	24.5	20.0	36.8	32.8	25.5	0.35	0.50
98	37.0	32.3	27.3	20.0	37.0	32.3	27.6	0.75	0.82
99	36.2	34.5	27.3	20.0	36.4	33.8	26.8	0.83	0.70
100	36.6	34.8	27.3	20.0	36.6	33.9	25.5	0.80	0.50

Average Umbilical-Foot Temperature Gradient before 6.8°C

Average Umbilical-Foot Temperature Gradient after 6.2°C

Average Reduction in Gradient 0.6°C

Average Thermal Circulation Index before 0.81

Average Thermal Circulation Index after 0.94

Ratio 1.16

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation.
	Before	After.		Before	After.	
86	5	8	-	76	84	+
97	3	5	-	88	84	+
98	4	4	+	84	84	+
99	4	3	+	64	64	+
100	4	3	-	76	92	+

Average pupil size before 4.0 mms.
 Average pupil size after 4.6 mms.
 Average change in pupil size +0.6 mms.

Accommodation paralysis 2

Average pulse rate before 77.6 per minute.
 Average pulse rate after 81.6 per minute.
 Average change in pulse rate +4.0 per minute.

Dry Mouth 0

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
86	100	200	2.00
97	25	75	3.00
98	20	85	4.25
99	150	200	1.33
100	27	45	1.66

Average Ratio 2.45

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After		Before	After	
64	5	5	-	64	64	+
69	5	4	-	64	96	+
80	3	3	+	76	80	-
72	3	5	+	80	80	+
70	5	5	-	68	72	+

Average pupil size before 4.2 mms.
 Average pupil size after 4.4 mms.
 Average change in pupil size +0.2 mms.

Accommodation Paralysis 2

Average pulse rate before 70.8 per minute.
 Average pulse rate after 78.4 per minute.
 Average change in pulse rate +7.6 per minute.

Dry Mouth 1

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
64	50	100	2.00
69	19	60	3.16
80	150	500	3.33
72	25	45	1.80
70	60	75	2.08

Average Ratio 2.47

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after	
		Erect	Recumbent	Erect	Recumbent
64	36	110/65	115/70	95/60	110/70
69	21	120/80	120/80	55/40	100/90
80	45	110/70	110/20	105/70	100/70
72	36	115/80	120/85	105/80	115/85
70	21	110/85	130/90	105/85	110/90

Average change in Recumbent diastolic pressure -2

Average change in Erect diastolic pressure -9

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C		Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index		
	Body	Umbilical		Foot	Body	Umbilical	Foot	Before	1 hr. after
64	36.6	34.0	31.0	19.0	36.6	31.6	31.6	2.25	2.60
69	36.4	32.2	23.0	19.0	36.4	29.6	25.5	0.30	0.60
80	36.6	32.3	30.3	20.0	36.6	30.0	30.2	1.70	1.60
72	36.6	34.2	28.5	20.5	36.6	33.2	27.6	1.00	0.80
70	36.4	32.6	27.0	19.0	36.4	32.0	23.3	0.88	0.33

Average Umbilical-Foot Temperature Gradient before 5.1°C

Average Umbilical-Foot Temperature Gradient after 3.6°C

Average Reduction in Gradient 1.5°C

Average Thermal Circulation Index before 1.23

Average Thermal Circulation Index after 1.19

Ratio 0.97

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after	
		Erect	Recumbent	Erect	Recumbent.
167	6	120/90	120/90	115/85	120/90
168	6	110/70	110/75	105/65	110/70
170	6	145/100	150/100	120/65	130/70
173	6	110/80	110/80	---	50/40
174	9	140/90	140/90	100/75	105/80

Average change in Recumbent diastolic pressure -17

Average change in Erect diastolic pressure Postural Fall

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after
167	36.2	33.3	29.3	17.5	36.2	34.0	28.8	1.75	1.55
168	36.4	31.0	27.5	17.5	36.4	31.5	29.5	1.15	1.80
170	36.2	32.5	30.0	17.0	36.2	31.5	29.5	2.20	1.90
173	36.6	34.2	27.2	18.2	36.6	34.2	27.4	0.98	1.00
174	36.6	33.6	28.6	18.2	36.6	33.6	29.5	1.30	1.60

Average Umbilical-Foot Temperature Gradient before 4.4 °C

Average Umbilical-Foot Temperature Gradient after 4.0 °C

Average Reduction in Gradient 0.4 °C

Average Thermal Circulation Index before 1.42

Average Thermal Circulation Index after 1.77

Ratio 1.25

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After.		Before	After	
168	3	3	+	72	68	+
168	2	3	-	88	88	-
170	3	3	-	86	80	+
173	4	5	-	72	74	+
174	5	6	+	78	78	-

Average pupil size before 3.2 mms.
 Average pupil size after 4.0 mms.
 Average change in pupil size +0.8 mms.

Accommodation Paralysis 2

Average pulse rate before 64.8 per minute.
 Average pulse rate after 77.6 per minute.
 Average change in pulse rate +12.8 per minute.

Dry Mouth 0

EFFECT UPON THE SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after.	
167	35	75	3.57
168	50	35	0.70
170	19	65	3.42
173	40	50	1.13
174	75	100	1.33

Average Ratio 2.03

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after.	
		Erect	Recumbent	Erect	Recumbent.
147	13	130/90	130/90	95/75	100/80
148	13	120/70	120/70	80/60	100/80
164	5	135/90	145/90	120/90	125/90
169	5	110/80	110/80	105/80	105/80
175	8	120/75	130/80	110/75	110/80
Average change in Recumbent diastolic pressure		0			
Average change in Erect diastolic pressure		-5			

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index.	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after
147	36.6	30.2	27.8	19.0	36.6	33.3	31.4	1.02	2.50
148	36.6	31.2	25.5	19.0	36.6	32.6	31.5	0.58	2.55
164	36.2	34.5	29.5	19.0	36.2	33.5	28.8	1.90	1.34
169	36.6	32.5	31.0	19.0	36.8	32.5	31.5	2.25	2.30
175	36.2	33.8	30.2	16.8	36.2	33.6	31.2	2.26	2.80
Average Umbilical-Foot Temperature Gradient before							3.0°C		
Average Umbilical-Foot Temperature Gradient after							2.2°C		
Average Reduction in Gradient							0.8°C		
Average Thermal Circulation Index before							1.60		
Average Thermal Circulation Index after							2.30		
Ratio							1.44		

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After		Before	After.	
147	3	5	-	72	92	+
148	3	4	+	88	96	+
164	3	3	-	72	72	+
169	2	2	-	92	80	+
175	3	4	+	76	78	-
Average pupil size before				2,8 mms.		
Average pupil size after				3.6 mms.		
Average change in pupil size				+0.8 mms.		
Accommodation Paralysis				2		
Average pulse rate before				80.0 per minute.		
Average pulse rate after				83.6 per minute.		
Average change in pulse rate				+3.6 per minute.		
Dry Mouth				1		

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms \times 1000		Ratio
	Before	1 hr. after	
147	19	45	2.36
148	50	50	1.00
164	20	45	2.25
169	22	60	2.72
175	27	35	1.29
Average Ratio			1.93

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after	
		Erect	Recumbent	Erect	Recumbent.
65	26	125/80	130/75	110/80	120/85
77	49	120/80	120/80	100/85	105/80
79	49	120/90	130/90	120/90	130/90
81	33	120/80	120/85	95/65	100/65
255	49	115/80	115/80	115/80	115/80

Average change in Recumbent diastolic pressure -2

Average change in Erect diastolic pressure -1

EFFECT UPON THE BODY TEMPERATURE AND PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index.	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after
	65	36.2	33.2		29.0	20.5	36.2	33.2	31.0
77	36.4	31.0	25.8	20.5	36.4	31.5	26.5	0.50	0.60
79	36.4	34.5	27.5	20.5	36.4	34.3	27.3	0.78	0.73
81	36.2	35.1	25.8	20.5	36.2	32.2	26.2	0.52	0.56
255	36.6	32.3	31.4	19.8	36.6	32.4	29.8	2.25	1.50

Average Umbilical-Foot Temperature Gradient before 5.5°C

Average Umbilical-Foot Temperature Gradient after 4.6°C

Average Reduction in Gradient 0.9°C

Average Thermal Circulation Index before 1.05

Average Thermal Circulation Index after. 1.10

Ratio 1.00

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute.		Salivation
	Before	After		Before	After	
65	3	6	+	80	84	+
77	3	4	+	72	68	+
79	3	5	+	84	72	+
81	2	3	-	76	84	-
255	3	3	-	84	92	+
Average pupil size before				2.8 mms.		
Average pupil size after				4.2 mms.		
Average change in pupil size				+1.8 mms.		
Accommodation Paralysis				2		
Average pulse rate before				79.2 per minute.		
Average pulse rate after				80.0 per minute.		
Average change in pulse rate				+1.2 per minute.		
Dry Mouth				1		

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after.	
65	220	300	1.36
77	30	150	5.00
79	23	40	1.30
81	25	100	4.00
255	19	25	1.42

Average Ratio 2.22

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug	
		Erect	Recumbent	Erect	Recumbent
30	22.5	105/65	105/65	105/65	105/65
33	22.5	105/85	125/90	110/90	110/90
35	30	105/95	115/80	105/95	120/85
39	30	120/80	120/80	110/85	110/75
45	30	110/85	110/75	115/80	115/80
Average change in Recumbent diastolic pressure				+2	
Average change in Erect diastolic pressure				+2	

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index		
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after	
30	36.2	33.5	28.0	21.2	36.2	33.5	28.1	0.85	0.86	
33	36.1	32.0	27.2	20.4	36.1	32.8	28.5	0.75	1.05	
35	36.4	33.0	28.5	20.2	36.4	33.0	28.5	1.05	1.05	
39	36.2	32.8	29.0	20.2	36.2	32.6	27.4	1.25	0.83	
45	36.6	33.0	25.5	19.8	36.6	32.5	25.5	0.51	0.51	
Average Umbilical-Foot Temperature Gradient before							5.2°C			
Average Umbilical-Foot Temperature Gradient after							4.9°C			
Average Reduction in Gradient					0.3°C					
Average Thermal Circulation Index before							0.88			
Average Thermal Circulation Index after							0.86			
Ratio					0.98					

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation.
	Before	After.		Before	After	
30	3	5	+	84	128	+
33	4	4	-	96	128	+
35	2	3	-	72	126	-
39	3	5	+	72	90	+
45	2	3	-	68	88	+
Average pupil size before			2.8 mms.			
Average pupil size after			4.0 mms.			
Average change in pupil size			+1.2 mms.			
Accommodation Paralysis			2			
Average pulse rate before			78.4 per minute.			
Average pulse rate after			112.0 per minute.			
Average change in pulse rate			+34.4 per minute.			
Dry Mouth			1			

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
30	55*	150	2.74
33	19	30	1.58
35	75	500	4.00
39	60	150	2.50
45	100	500	5.00
Average Ratio			3.16

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after	
		Erect	Recumbent	Erect	Recumbent
5	38	120/90	135/90	115/70	105/70
6	19	125/80	130/80	105/70	120/80
9	76	110/70	110/70	110/70	110/70
23	38	115/80	120/80	110/70	115/80
87	76	120/95	130/95	120/95	130/95
Average change in Recumbent diastolic pressure		-4			
Average change in Erect diastolic pressure		-8			

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after.
5	36.8	32.0	30.0	21.0	36.8	32.5	27.0	1.30	0.60
6	36.8	32.5	32.5	21.0	36.8	33.5	31.5	2.70	2.00
9	37.0	34.0	30.5	21.0	37.0	33.2	29.5	1.45	1.15
23	36.4	33.5	32.0	19.8	36.4	31.3	29.5	2.80	1.38
87	36.4	32.5	26.5	19.0	36.4	32.0	26.5	0.75	0.75
Average Umbilical-Foot Temperature Gradient before							2.6°C		
Average Umbilical-Foot Temperature Gradient after							3.7°C		
Average Increase in Gradient				1.1°C					
Average Thermal Circulation Index before							1.80		
Average Thermal Circulation Index after							1.18		

Ratio 0.66

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After		Before	After	
5	7	6	-	76	86	+
6	6	6	-	80	80	+
9	8	8	-	64	60	+
23	4	3	-	72	64	+
87	4	3	-	88	84	+

Average pupil size before 5.8 mms.
 Average pupil size after 5.2 mms.
 Average change in pupil size -0.6 mms.

Accommodation Paralysis 0

Average pulse rate before 76.0 per minute.
 Average pulse rate after 81.6 per minute.
 Average change in pulse rate +5.6 per minute.

Dry Mouth 0

EFFECT UPON THE SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
5	500	300	0.60
6	90	80	0.89
9	75	75	1.00
23	50	100	2.00
87	90	180	2.00

Average Ratio 1.30

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug.	
		Erect	Recumbent	Erect	Recumbent.
3	15	120/80	120/80	115/75	95/75
8	60	135/95	130/100	120/95	125/95
10	60	110/80	105/75	100/75	90/65
189	60	120/80	120/80	115/75	115/75
193	60	110/75	110/75	115/70	110/70
Average change in Recumbent diastolic pressure				-4	
Average change in Erect diastolic pressure				-6	

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index.	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after.
3	36.8	34.2	29.5	21.0	36.8	32.8	28.0	1.16	0.79
8	36.8	33.0	29.5	21.0	36.2	33.8	32.5	1.65	3.20
10	36.2	32.8	30.0	20.2	36.2	32.6	29.6	1.60	1.40
189	36.2	34.5	30.5	20.2	36.2	33.8	32.5	1.65	3.20
193	36.2	34.1	29.2	20.2	36.2	33.8	29.4	1.30	1.36
Average Thermal Circulation Index before							1.37		
Average Thermal Circulation Index after							1.57		

Ratio 1.15

Average Umbilical-Foot Temperature Gradient before	4.0°C
Average Umbilical-Foot Temperature Gradient after	3.5°C
Average Reduction in Gradient	0.5°C

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After.		Before	After	
3	5	5	-	60	60	+
8	6	4	-	88	68	+
10	6	7	-	72	80	+
189	4	3	-	72	80	+
193	3	4	-	84	80	+

Average pulse rate before 75.6 per minute.

Average pulse rate after 69.6 per minute.

Average change in pulse rate -6.0 per minute.

Accommodation Paralysis 0

Average pupil size before 4.9 mms.

Average pupil size after 4.6 mms.

Average change in pupil size -0.2 mms.

Dry Mouth 0

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
3	20	30	1.50
8	35	40	1.14
10	50	35	0.70
189	75	50	0.66
193	150	200	1.33

Average Ratio 1.07

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug	
		Erect	Recumbent	Erect	Recumbent
14	30	125/80	125/80	130/90	130/90
16	100	105/70	110/70	100/70	110/70
17	30	110/70	110/70	105/65	105/65
19	50	125/70	130/70	120/85	120/85
88	65	110/80	110/80	130/80	130/90

Average change in Recumbent diastolic pressure +6

Average change in Erect diastolic pressure +4

EFFECT UPON THE BODY TEMPERATURE AND PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after
14	36.4	33.0	27.5	20.0	36.4	33.5	25.2	0.85	0.48
16	36.4	33.0	30.5	20.0	36.4	33.5	30.5	1.80	1.80
19	36.6	33.8	28.5	20.0	36.6	33.2	28.8	1.06	1.14
88	36.6	33.8	29.3	21.5	36.6	34.5	28.3	1.08	0.82

Average Umbilical-Foot Temperature Gradient before 4.2°C

Average Umbilical-Foot Temperature Gradient after 5.1°C

Average Increase in Gradient 0.9°C

Average Thermal Circulation Index before 1.41

Average Thermal Circulation Index after 1.17

Ratio 0.83

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After.		Before	After	
16	4	5	-	70	80	+
14	7	4	-	80	60	+
17	6	3	-	76	68	+
19	4	3	-	80	68	+
88	4	4	+	68	68	+
Average pupil size before			5.0 mms.			
Average pupil size after			3.8 mms.			
Average change in pupil size			-1.2 mms.			
Accommodation Paralysis			1			
Average pulse rate before			74.8 per minute.			
Average pulse rate after			68.8 per minute.			
Average change in pulse rate			-6.0			
Dry Mouth			0			

EFFECT UPON SWEAT GLAND SECRETION.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
14	19	19	1.00
16	100	100	1.00
17	75	75	1.00
19	15	18	1.20
88	20	22	1.10

Average Ratio 1.08

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug	
		Erect	Recumbent	Erect	Recumbent
51	0.5	110/85	110/85	110/85	110/85
53	0.5	110/85	120/90	110/75	115/80
54	0.5	120/90	125/90	110/75	110/80
55	0.5	105/65	100/60	90/70	100/65
56	0.5	110/70	105/70	110/70	115/70

Average change in Recumbent diastolic pressure -3

Average change in Erect diastolic pressure -4

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after
51	36.4	31.5	27.5	16.5	36.4	32.0	26.4	1.25	1.00
53	36.4	32.3	22.5	16.5	36.4	31.0	22.5	0.44	0.44
54	36.2	33.0	28.2	16.5	36.2	31.5	24.8	1.45	0.75
55	35.4	32.6	26.0	16.5	36.4	31.8	25.6	1.00	0.85
56	36.2	32.2	24.8	16.5	36.2	31.8	26.8	0.74	1.10

Average Umbilical-Foot Temperature Gradient before 6.5°C

Average Umbilical-Foot Temperature Gradient after 6.4°C

Average Reduction in Gradient 0.1°C

Average Thermal Circulation Index before 0.98

Average Circulation Index after 0.83

Ratio 0.85

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation.
	Before	After.		Before	After	
51	3	3	-	68	68	+
53	3	5	+	68	76	+
54	3	4	-	80	80	-
55	3	3	-	64	72	+
56	3	4	-	60	64	-

Average pupil size before 3.0 mms.
 Average pupil size after 3.8 mms.
 Average change in pupil size +0.8 mms.

Accommodation Paralysis 1

Average pulse rate before 68.0 per minute.
 Average pulse rate after 72.0 per minute.
 Average change in pulse rate +4.0 per minute.

Dry Mouth 2

2.11

2.1 Circulation Index
 re 1 hr. after

3.77

EFFECT UPON THE SWEAT GLAND ACTIVITY

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after.	
51	19	35	1.84
53	100	300	3.00
54	100	100	1.00
55	75	200	2.67
56	50	90	1.80
Average Ratio			2.06

0.80

0.80

1.06

0.93

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug.	
		Erect	Recumbent	Erect	Recumbent.
184	1	130/75	130/75	125/70	130/85
187	4	125/80	120/80	125/75	120/75
197	4	120/75	120/75	125/80	125/80
210	3	115/75	120/80	115/70	115/75
217	7	110/80	125/85	110/75	120/80
Average change in Recumbent diastolic pressure		0			
Average change in Erect diastolic pressure		-3			

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after.
184	36.8	33.8	27.2	19.2	36.8	33.6	26.8	0.84	0.77
187	36.6	34.2	27.0	19.2	36.6	34.2	26.8	0.82	0.80
197	36.6	33.6	25.8	19.4	36.6	31.4	27.2	0.60	0.84
210	36.4	32.6	29.6	19.4	36.4	31.8	28.8	1.48	1.26
217	36.6	34.2	25.8	19.0	36.6	33.6	27.4	0.64	0.93
Average Umbilical-Foot Temperature Gradient before							6.6°C		
Average Umbilical-Foot Temperature Gradient after							5.5°C		
Average Reduction in Gradient				1.1°C					
Average Thermal Circulation Index before							0.88		
Average Thermal Circulation Index after							0.92		
Ratio				1.05					

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After		Before	After	
184	3	6	+	66	84	-
187	3	5	+	72	96	-
197	3	6	+	70	96	-
210	4	7	-	68	120	+
217	3	5	+	66	92	-
Average pupil size before				3.2 mms.		
Average pupil size after				5.8 mms.		
Average change in pupil size				+2.6 mms.		
Accommodation Paralysis				4		
Average pulse rate before				68.4 per minute.		
Average pulse rate after				77.6 per minute.		
Average change in pulse rate				+9.4 per minute.		
Dry Mouth				1		

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after	
184	50	150	3.00
187	75	200	2.67
197	35	80	2.29
210	40	90	2.25
217	35	60	1.71

Average Ratio 2.38

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug.	
		Erect	Recumbent	Erect	Recumbent.
20	26	105/75	110/70	105/75	110/75
22	35	120/90	120/90	120/90	125/90
24	35	110/80	110/80	115/90	120/85
27	35	110/70	115/70	110/75	115/80
253	16	105/75	105/75	85/65	95/70
Average change in Recumbent diastolic pressure				+3	
Average change in Erect diastolic pressure				+1	

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after.
20	36.6	33.0	29.5	19.5	36.6	32.5	30.3	1.40	1.75
22	36.4	33.0	29.0	19.5	36.4	33.0	28.2	1.28	1.04
26	36.2	34.2	28.0	19.5	36.2	33.5	27.3	1.04	0.86
27	36.8	31.8	31.9	19.5	36.8	32.0	32.0	1.95	3.65
253	36.6	33.2	27.2	19.8	36.6	34.0	27.2	0.78	0.78
Average Umbilical-Foot Temperature Gradient before							3.9°C		
Average Umbilical-Foot Temperature Gradient after							4.0°C		
Average Increase in Gradient							0.1°C		
Average Thermal Circulation Index before							1.29		
Average Thermal Circulation Index after							1.62		
Ratio							1.16		

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation.
	Before	After		Before	After	
20	3	8	+	68	96	+
22	5	6	-	76	102	-
26	4	3	+	104	120	-
27	3	6	+	80	96	+
256	3	4	-	60	76	-

Average pupil size before 3.6 mms.
 Average pupil size after 5.4 mms.
 Average change in pupil size +1.8 mms.

Accommodation Paralysis 3

Average pulse rate before 77.6 per minute.
 Average pulse rate after 98.0 per minute.
 Average change in pulse rate +20.6 per minute.

Dry Mouth 2

EFFECT UPON SWEAT GLAND ACTIVITY.

No.	Skin Resistance in ohms x 1000		Ratio
	Before	1 hr. after.	
20	30	150	5.00
22	20	150	7.50
26	19	25	1.42
27	200	500	2.50
253	5000	600	1.20

Average Ratio 3.52

EFFECT UPON THE BLOOD PRESSURE.

No.	Dose of cation mg. subcutaneous	Blood Pressure mms. Hg.			
		Before		1 hr. after drug.	
		Erect	Recumbent	Erect	Recumbent.
42	36	110/80	110/80	105/80	105/80
43	36	110/80	110/75	110/85	115/80
44	36	120/95	120/95	120/95	120/95
47	36	120/80	130/85	100/80	120/80
48	36	115/75	110/80	115/70	110/80

Average change in Recumbent diastolic pressure 0

Average change in Erect diastolic pressure 0

EFFECT UPON THE BODY TEMPERATURE AND THE PERIPHERAL CIRCULATION.

No.	Before. Temp. °C			Room Temp. °C	1 hr. after. Temp. °C			Thermal Circulation Index.	
	Body	Umbilical	Foot		Body	Umbilical	Foot	Before	1 hr. after
	42	36.8	32.5		27.0	16.0	36.8	32.5	24.4
43	36.6	31.3	27.8	16.0	36.6	32.0	26.8	1.38	1.13
44	37.0	31.6	23.0	16.0	37.0	31.5	22.5	0.50	0.46
47	36.6	35.0	26.0	16.0	36.6	34.5	25.3	0.97	0.84
48	37.2	34.3	25.3	16.0	37.2	32.5	24.5	0.78	0.68

Average Umbilical-Foot Temperature Gradient before 7.1°C

Average Umbilical-Foot Temperature Gradient after. 7.9°C

Average Increase in Gradient 0.8°C

Average Thermal Circulation Index before 0.95

Average Thermal Circulation Index after 0.76

Ratio 0.80

EFFECT UPON THE PUPIL AND ACCOMMODATION, PULSE RATE AND SALIVATION.

No.	Pupil Size mms.		Accommodation Paralysis	Pulse / minute		Salivation
	Before	After		Before	After	
42	3	3	-	68	112	+
43	3	5	+	72	96	0
44	3	3	-	84	108	0
47	3	4	-	72	120	0
48	3	3	-	52	88	0

Average pupil size before 3.0 mms.
 Average pupil size after 3.6 mms.
 Average change in pupil size +0.6 mms.

Accommodation Paralysis 4

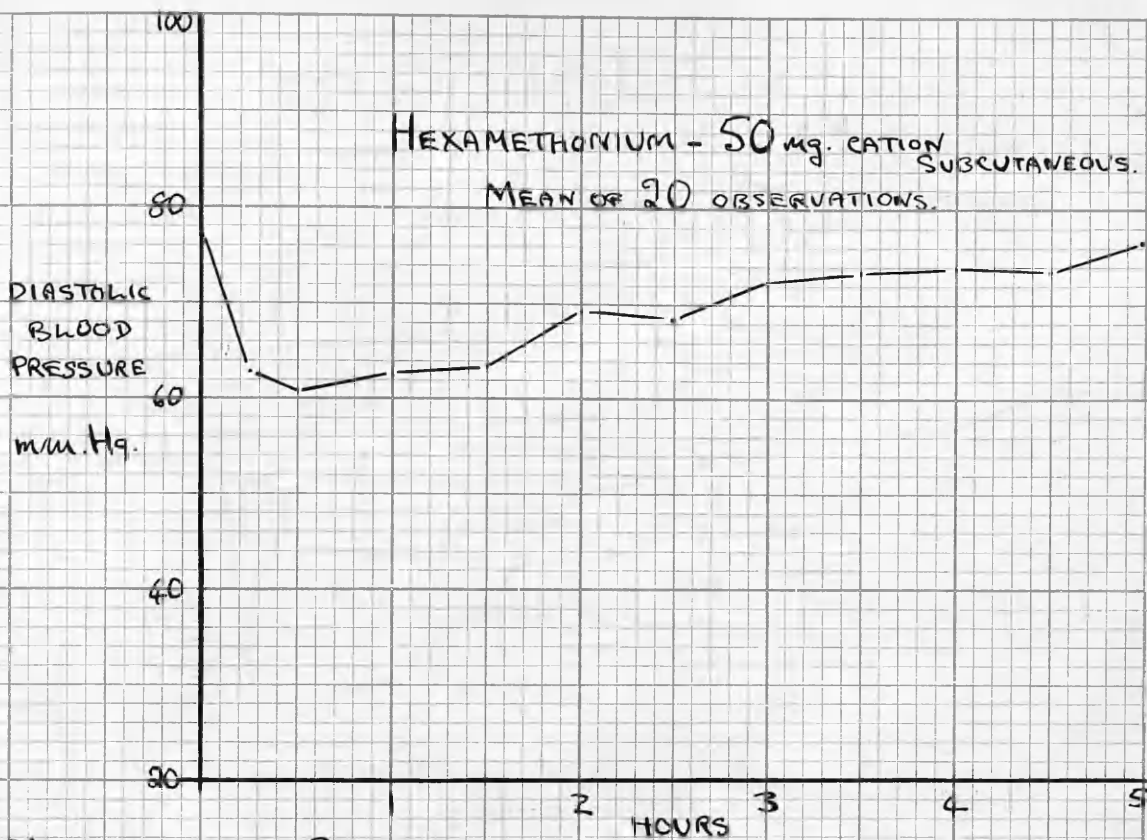
Average pulse rate before 69.6 per minute.
 Average pulse rate after 104.8 per minute.
 Average change in pulse rate +35.2 per minute.

Dry Mouth 4

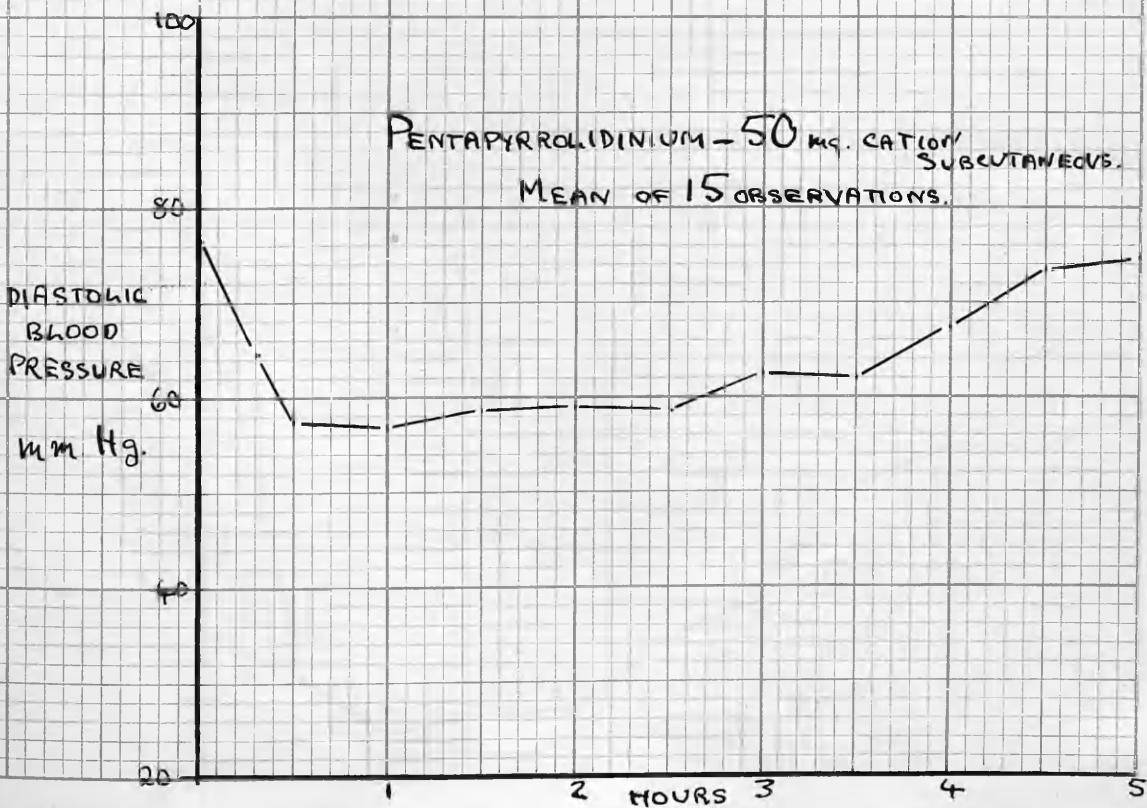
EFFECT UPON SWEAT GLAND ACTIVITY.

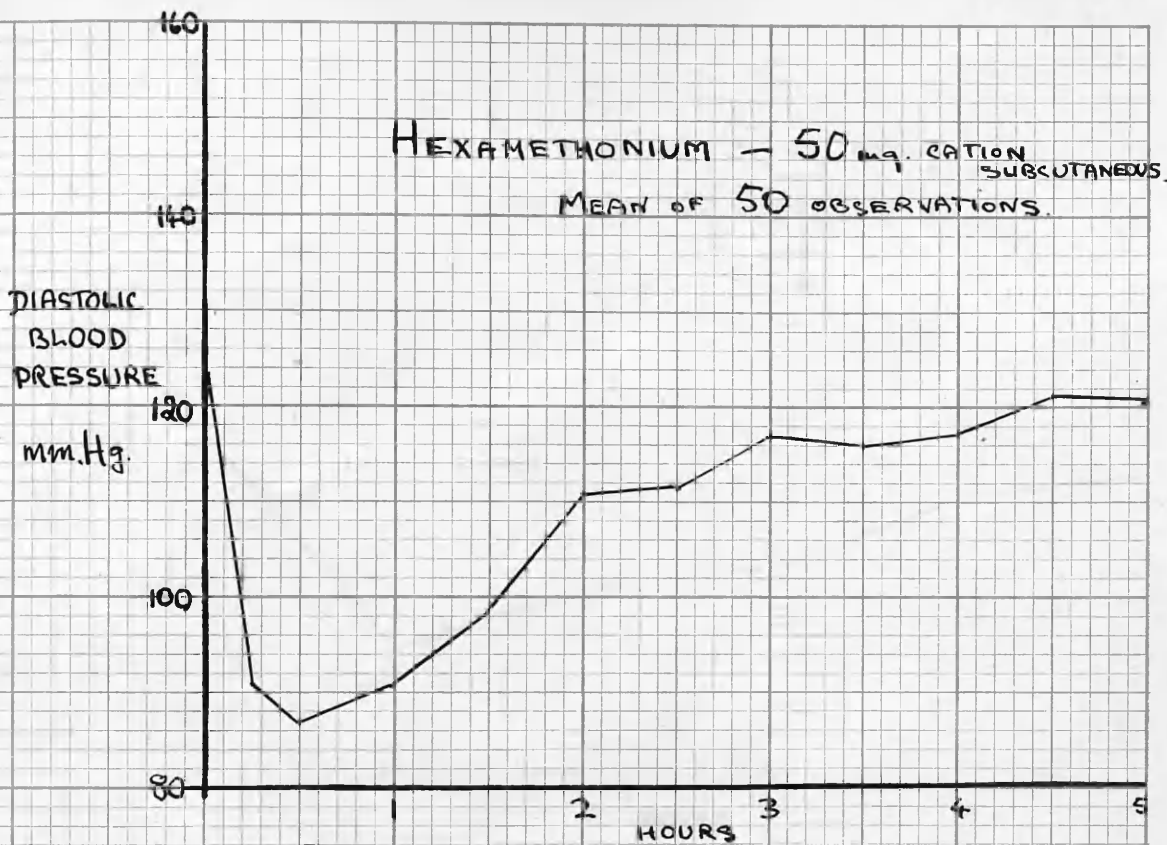
No.	Skin Resistance in ohms x 1000		Ratio
	Before	4 hr. after	
42	95	500	5.26
43	75	250	3.33
44	35	75	2.14
47	95	1000	10.50
48	80	500	6.25

Average Ratio 5.50

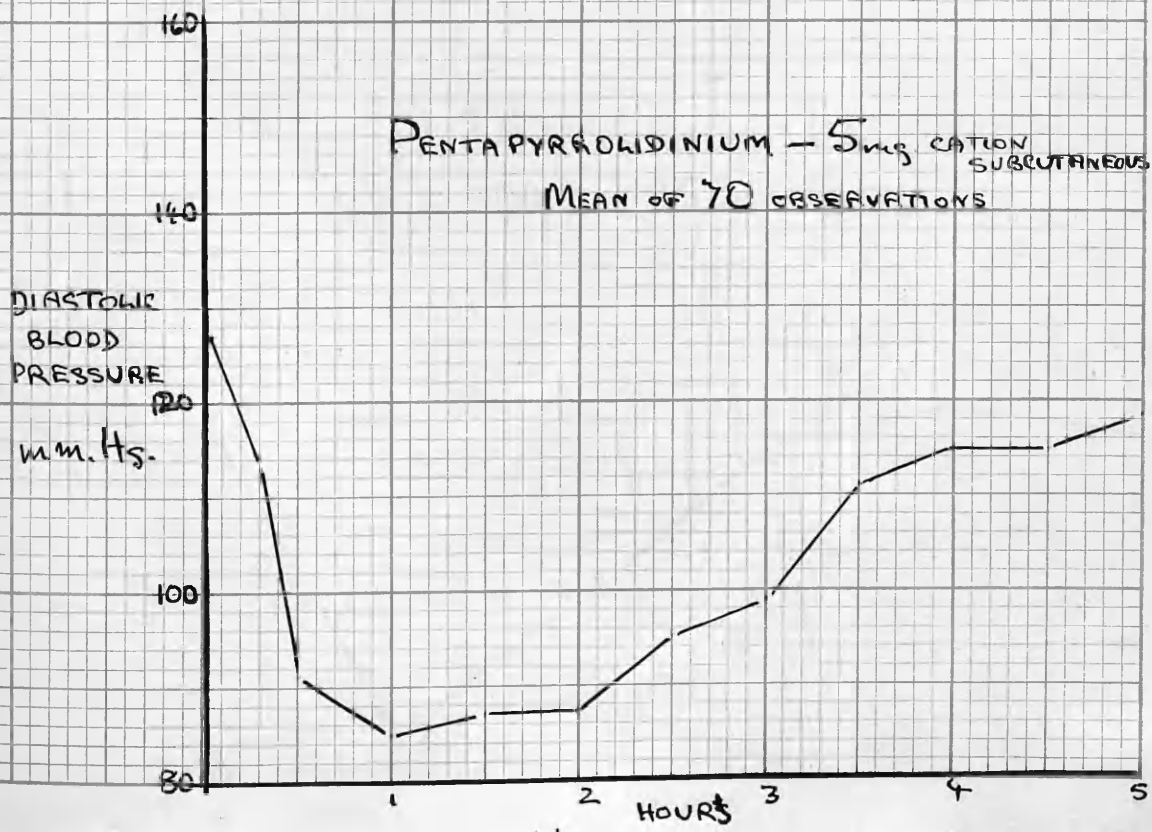


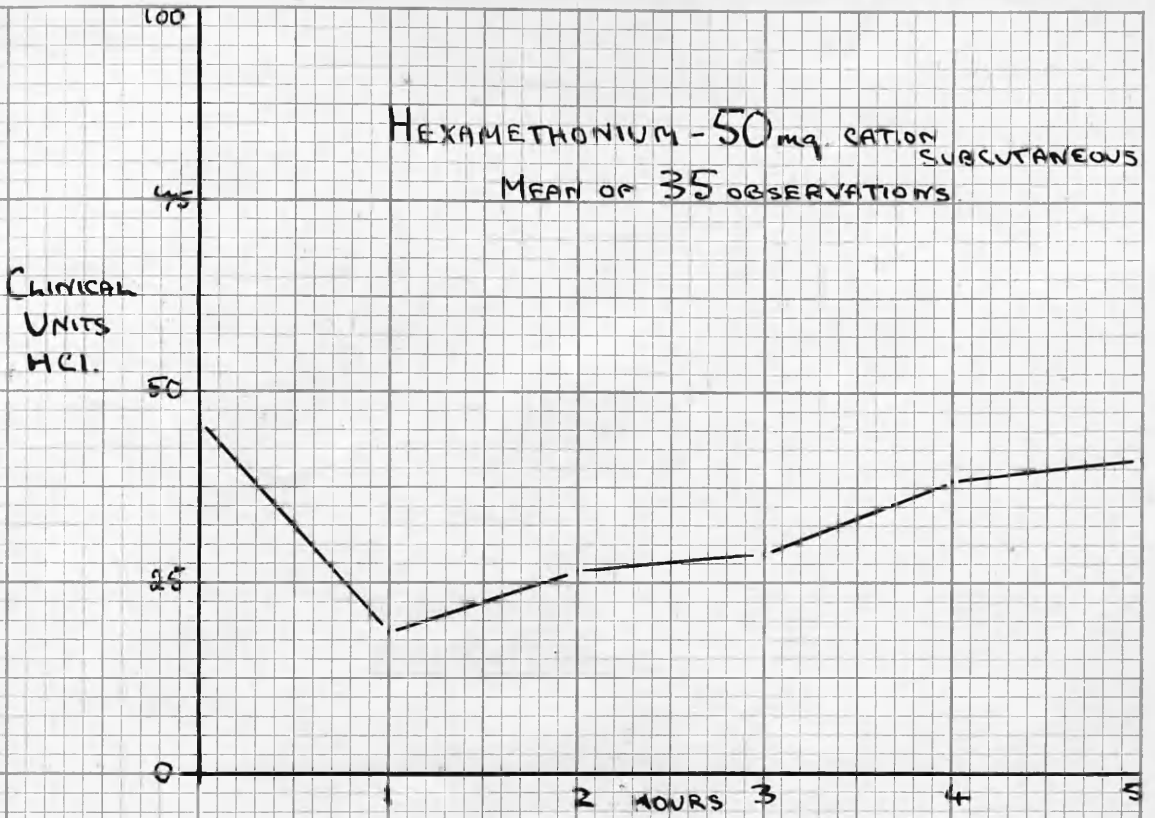
NORMOTENSIVE PATIENTS.
RECUMBENT



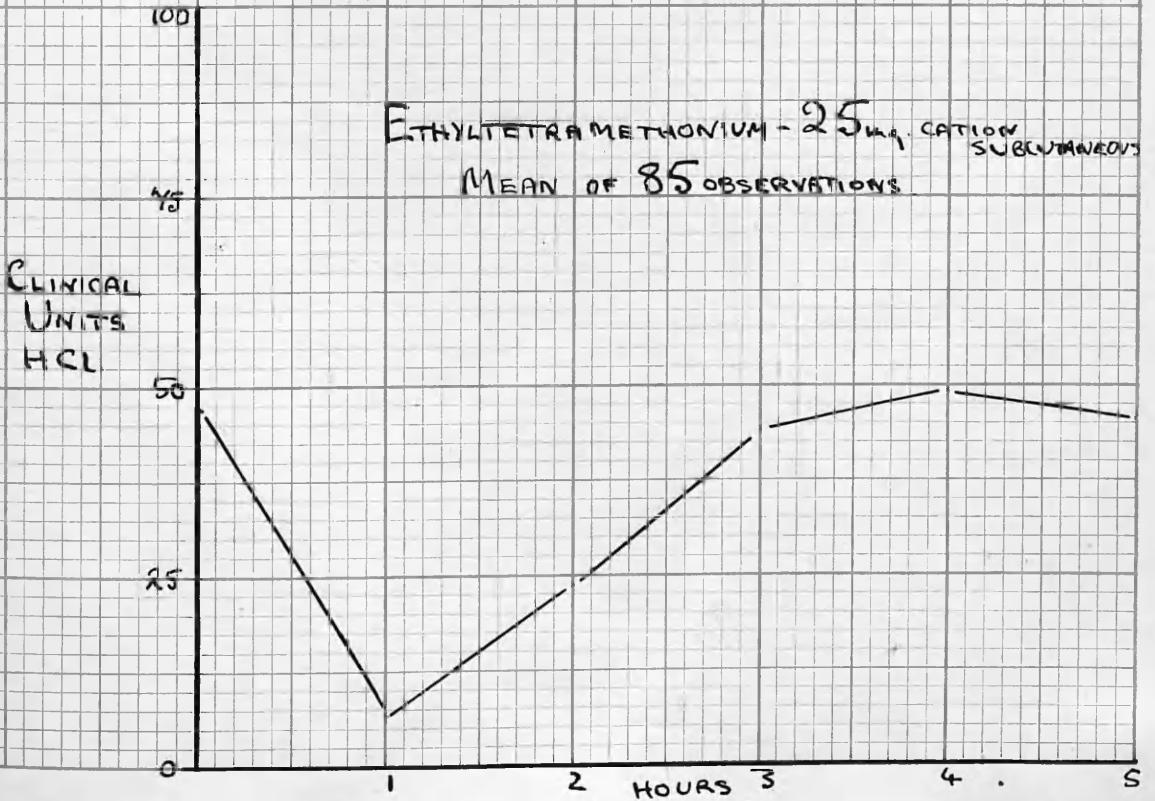


HYPERTENSIVE PATIENTS
RECUMBENT





HYPERCHLORHYDRIC PATIENTS.



PUBLICATIONS

ETHYL TETRAMETHONIUM IN THE CONTROL

OF GASTRIC SECRETION.

R. D. H. Maxwell, B. Sc., M. B., Ch. B., Junior
Hospital Medical Officer,

A. J. M. Campbell, M. B., Ch. B., F. R. F. P. S. G.,
Medical Registrar,

THE ROYAL ALEXANDRA INFIRMARY, PAISLEY.

ETHYLTETRAMETHONIUM IN THE CONTROL OF GASTRIC SECRETION

A major part of the research into the medical treatment of duodenal ulceration consists of the development of drugs which depress the secretomotor activity of the stomach. Atropine is commonly employed for this purpose, but it is recognised that this alkaloid is inconstant in action and produces marked side effects, mainly consisting of dryness of the mouth and blurring of vision. During the last four years we have been interested in the synthesis of a large number of new compounds affecting the autonomic nervous system. We have selected two, upon a basis of previous experience, for examination in comparison with the known activity of atropine and hexamethonium, and we have included, in addition, certain other new drugs. A group of 100 patients suffering from proven duodenal ulceration with hyperchlorhydria was chosen for this comparative study.

These new compounds all modify the synaptic transmission of the vagus and they can be divided into two groups, those which resemble atropine in having their main activity at the peripheral synapse, and those which block the ganglionic synapse.

Atropine-like substances

Methantheline (Banthine) has been used widely in America, its actions having been described by Longino et al. (1950), and others.

Dibutoline, which has been investigated by Lorber and Machella (1950), and others, has a similar activity but is active only by parenteral

injection. In France, Camelin et al. (1952) have used thiazinamium. Iachesine was made by Ing (1946) as a synthetic atropine.

Ganglion-blocking Agents

Tetra-ethyl-ammonium was demonstrated to inhibit gastric activity but the results were vitiated by the side effects characteristic of this compound. A major advance was made by Kay and Smith (1950) who used hexamethonium. They showed that this drug was capable of producing gastric inhibition of useful duration. However, Douthwaite and Thorn (1950) indicated that dosage of this drug sufficient to affect gastric activity even in normotensive patients could not be given without a high incidence of severe postural hypotension.

The biological investigation of bisthiazinamium by Ducrot and Decourt (1950) and 2512F by Bulbring and Depierre (1949) suggested their inclusion. The C.3 of the latter series, phenoxytrimethonium, is described here, as it is more active.

We were interested particularly in the comparative activity of the two new synthetic compounds which we had found previously (1953) inhibited gastric secretomotor activity in dosage significantly smaller than that required to lower the blood pressure. They are ethyltetramethonium and hexapyrrolidinium.

Ethyltetramethonium is the bis-diethylmethyl homologue of tetramethonium. With Graham (1952) we have previously described the action

in man of the bis-dimethylethyl homologue of hexamethonium. Hexa-pyrrolidinium is the bis-pyrrole homologue of hexamethonium. Clinical pharmacology of the penta compound of this series, a potent hypotensive agent, has already been described by us (1953), and by Smirk (1953).

Methods of Investigation

It was decided to investigate the action of these drugs in depressing basal vagal tone, so the technique adopted consisted of frequent aspiration of the contents of the fasting stomach, using stimuli in the form of alcohol test meals, histamine, and acetyl-B-methylcholine to extend observations only. Levin et al. (1951) agree upon the usefulness of this method. It was noted at an early stage that first aspiration sequences upon individual patients were of little value as the results were influenced by the novelty of the experience. Only when members forming a group of 4 to 10 patients met in different rotation two or three times per week was it possible to obtain consistent results from individual patients, and then only by the second to fourth day of attendance, when conditioning to intubation had occurred. From a total of 127 patients suffering from duodenal ulceration it was possible to select 100 who produced fairly constant fasting free acid levels of the order of 20-50 clinical units.

Control observations were made routinely, injecting sterile water subcutaneously or down the Ryle's tube, according to the method of

drug administration used at the time. No significant fluctuation of acidity followed the use of sterile water. There was some variation from day to day and over a period of months in acid levels. The 27 patients excluded comprised those who had low acid levels, very high acid levels, or who produced excessively large or excessively small volume of secretions. Those who showed gross day to day variation in secretion were also excluded. Simpson (1954) has shown that to observe the effect of drugs upon unselected normal and dyspeptic patients leads to variations in response, to an extent which makes interpretation difficult.

Each observation sequence consisted of the attendance of a group of out-patients from 9 a.m. until 1 p.m. on two or three occasions per week. The stomach was emptied as far as possible at hourly intervals. The drug was injected subcutaneously in aqueous solution at the end of the first hour, except in later observations when injected by the Rhile's tube, and one hour allowed for absorption.

Rotation of the drugs used was necessary to minimise the effects of individual degrees of susceptibility and acquisition of tolerance. One hour before and one hour after drug administration, the blood pressure was measured in the recumbent and then the erect posture. The pulse rate, the umbilical-toe temperature gradient, the skin resistance and the pupil size were recorded. Complaints of inability to read small print and of dryness of the mouth were noted.

The volume of each gastric specimen was measured, and free

hydrochloric acid content was estimated by titration against N 10 sodium hydroxide using Topffer's reagent as indicator. The pH of each specimen was measured by a Marconi pH meter. Even in a small investigation such as this, 810 observation sequences were required during the preliminary evaluation. This involved 3,274 individual titrations and 2,421 pH estimations. *by whom?*

Clinical Results:

The results obtained with both groups of compounds are shown in summarised form in Figures I and II. Dosage is expressed in cation, as a variety of salts was used. The gastric effective dose shows the subcutaneous mg. of cation which produced achlorhydria in 60 of initial doses. In the case of some of these drugs, consistency of action upon the stomach to this extent could not be obtained without producing severe side actions. The gastric effective dose is therefore described as over the dosage used.

In determining the usefulness of these drugs, the relative quantity of the effective dose is not of importance provided it can be administered conveniently, the comparative severity of side actions being the essential method of assessment.

Examination of Figure I shows that the last three drugs are more consistent in action than atropine, but their dosage is accompanied by side actions in excess of those produced by atropine. The severe tachycardia produced by methantheline is less pronounced when this drug is given orally. Its high activity in inhibiting sweat secretion is to be noted.

The results obtained with four new ganglion-blocking agents recorded in Figure II show that all of these produce less marked side actions than hexamethonium. The side actions of the last two were negligible, but a dosage level capable of producing consistent depression of gastric secretion could not be reached, owing to the large volume of injection required. It is of some interest to note that phenoxytrimethonium produced consistently a slight increase in the recorded blood pressures.

Of the two new drugs which we have described already, ethyltetramethonium produced rather more satisfactory results. During 47 further observations upon hexapyrrolidinium, and upon using it in repeated dosage, blurring of vision and headaches were encountered and there was a suggestion of a cumulative action in depressing the blood pressure. Subsequent observations were therefore confined to ethyltetramethonium. As can be seen from Figure II, ethyltetramethonium in one half the parenteral dose of hexamethonium was as consistent in action in depressing gastric secretion, while its side actions, other than inhibition of sweat secretion, were much less pronounced. In comparison with atropine, it is more consistent in action, and side effects are minimal. The duration of actions is shorter than that of hexamethonium; and the depression of acid secretion, although greater than that produced by atropine, is less profound than that which is obtainable with hexamethonium, which is accompanied, however, by hypotension.

In Figure III, the effect of 25 mg. of ethyltetramethonium (mean of 75 observations) upon the fasting level of acid secretion is shown in comparison with 50 mg. of hexamethonium (mean of 20 observations) and 2 mg. of atropine (mean of 10 observations), again in single subcutaneous dosage. The side actions of ethyltetramethonium in this series of observations were negligible. In 40% of these observations, hexamethonium produced a fall in the diastolic blood pressure incompatible with the maintenance of consciousness in the static erect posture; and, in every case, complaints of dryness of the mouth and blurring of vision followed dosage of atropine.

Ethyltetramethonium was found to modify alcohol test meals and to inhibit gastric motility, the effect being shorter than previously described with hexamethonium. Its action was reversed by acetyl-B-methylcholine and by histamine.

In oral dosage, its consistency of action was greater than that of hexamethonium and atropine, the duration of action being shorter than that of hexamethonium. The results obtained in oral and subcutaneous dosage are shown in Figure IV.

Ethyltetramethonium is chemically closely similar to hexamethonium, and, in common with it, no long-term toxicity has been found. The inhibition of motility which it produces may possibly lead to an ileus during sustained heavy dosage, but this has not occurred in our experience as a complication to treatment.

It is noteworthy that, during the period of test observations

extending in each patient to several months, all the patients became symptom-free, enabling a cautious suggestion to be made that depression intermittently of excessive gastric secretomotor activity, even to a moderate extent, may be a useful therapeutic measure in these cases. Several patients relapsed three months or longer after withdrawal of the test doses.

By intermittent dosage of ethyltetramethonium, usually for periods of up to three weeks, in total divided dosage of up to 19 daily as tolerance is acquired, it has been possible to suppress symptoms in a number of patients. In some it has been found adequate to use a single dose of 100 - 400 mg. at night.

Side actions have been confined to some mydriasis, rarely, blurring of vision, occasional dryness of mouth, and, occasionally, in individual cases, slight postural hypotension.

Discussion

In recent years, the usual techniques of estimation of gastric acidity by fractional test meals of the gruel or alcohol type have tended to lose repute. In the course of this investigation, we have found that this is largely due to the anxiety and discomfort which inevitably accompany the passage of a Ryle's tube and its retention in position. If the patient is accustomed to the technique, reliable results are frequently obtained. If fasting specimens only are withdrawn, the majority of patients with duodenal ulceration have levels of free acid of the order of 20-50 clinical units, which levels

are substantially higher than the usual fluctuation between zero and 30 units in the normal person. This hyperchlorhydria provides an indication of increased basal gastric vagal tone and the value of compounds which may affect vagal transmission can be determined, especially in comparison with known standards by the reduction of the hyperchlorhydria which the produce.

It is not readily possible to relate biological experimentation directly to clinical results; e.g. in the cat, ethyltetramethonium was found initially to have a greater sympathicolytic than vagolytic action. As wide a range of drugs of potential activity should therefore be examined to determine their range of activity in man.

Owing to variations in individual susceptibility and other factors, a fairly extensive investigation is required, but the difficulties involved in this are not comparable with those encountered in a therapeutic assay.

From the results of our investigation, ethyltetramethonium has emerged as a ganglion blocking agent, with minimal atropine-like side effects, which differs from the unselectively active hexamethonium in producing inhibition of gastric secretomotor activity in dosage approximately quarter of that required to produce hypotension. From limited observations it appears that oral dosage of this drug will control the symptoms of a number of patients with duodenal ulceration. In some cases, dosage at night has been adequate.

Summary

The effect of ten drugs in depressing the fasting acid of secretion of the stomach has been determined. A new ganglion blocking agent, ethyltetramethonium, has been found to depress gastric acidity in dosage which, in contrast with hexamethonium, does not affect the blood pressure, while atropine-like side effects are minimal. Its use as a substitute for atropine in the treatment of peptic ulceration, is suggested.

Acknowledgments:

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Figure I.

Drug	Gastric effective dose. mg. cation	Side actions, expressed as atropine 1.0		
ATROPINE	Over 2	Tachycardia	Mydriasis	Dry Skin
LACHESINE	Over 10	1.0	1.8	1.2
THIAZINAMIUM	30	2.4	1.0	1.4
DIBUTOLINE	40	2.0	1.2	1.5
METHANTHELINE	50	3.0	0.5	2.2

The side actions of four new drugs of atropine-like action compared with atropine in single subcutaneous dosage.

FIGURE II

Drug	Gastric Effective Dose mg. cation	Side Actions expressed as hexamethonium 1.0			
		Hypo- tension	Tachycardia	Mydriasis	Dry Skin
hexamethonium	50				
ethyltetra- methonium	25	0.10	0.25	0.15	0.90
hexapyrroli- dinium	25	0.20	0.50	0.30	1.20
Bis-thiazin- anium	over 100	0.05	0.75	0.0	0.40
Phenoxytri- methonium	over 150	0.0	0.0	0.0	0.25

The side actions of four new ganglion-blocking agents compared with hexamethonium in single subcutaneous dosage.

FIGURE III

Average increases in pH following a single subcutaneous injection of:

- 1) E. T. M. - Ethyltetramethonium 25 mg.
- 2) C. 6 - Hexamethonium 50 mg.
- 3) A - Atropine 2 mg.

FIGURE IV

Drug	Dose of Cation in mg.		Number of observations.		Percentage in which achlorhydria occurred	
	Subcutaneous	Oral	Subcutaneous	Oral	Subcutaneous	Oral
ethyltetra- methonium	25	100	75	50	61	38
hexamethonium:	50	500	20	50	85	34
atropine	2	20	10	20	40	10

The percentage of observations during which achlorhydria followed an initial dose of each drug subcutaneously and orally is shown, with the dosage in mg. of cation, and the number of observations made.

THE MEDICAL TREATMENT OF HYPERTENSION

J. Gibson Graham, M.D., F.R.F.P.S.G.,
Senior Physician.

R.D.H. Maxwell, B.Sc., M.B., Ch.B.,
Junior Hospital Medical Officer.

THE ROYAL ALEXANDRA INFIRMARY, PAISLEY.

THE MEDICAL TREATMENT OF HYPERTENSION

The survey by Master et al in 1943 showed that 30 to 40 per cent. of subjects over forty years of age, and 65 to 75 per cent. of those over seventy years of age, have hypertension. It is well recognised that the prognosis is good in the majority of cases, but in many instances hypertension is followed by an increasing degree of disability which merits active therapy. The fact that hypertension, in itself, is frequently compatible with a normal life expectation, tends to obscure its high mortality in those who develop symptoms. In his study of one thousand patients, Beehgaard (1946), found that 41 per cent. of males and 22.4 per cent of females died within five to ten years from the onset of symptoms.

It is essential to have an acceptable definition of hypertension. Wood (1950), has defined the limits of normal blood pressure as 145/90 mm. of mercury, stating the precautions necessary in recording this. Systolic hypertension in the young is usually a response to emotion and exercise; in older subjects, it is an indication of loss of elasticity of major arteries, and there are other causes. In essential hypertension, it is the increase in the diastolic blood pressure which is significant, and this is the pressure to which reference is made subsequently in this review. In our survey we have examined patients presenting with a diastolic pressure of 100 mm. and over. Four years ago, a new drug, hexamethonium, was placed

at our disposal, and for the first time, we found we had a reasonably certain method of reducing the level of the diastolic pressure to an extent greater than the response to general methods of treatment. It is therefore opportune to review our experience with hypertension over these four years, having particular regard to its treatment.

It is of interest to attempt to correlate the manifestations of hypertension in man with experimentally-induced hypertension. Page (1949), has comprehensively reviewed the methods of production of hypertension in animals. The types of greatest interest in relation to the pathogenesis of hypertension in man are the hypertension which follows renal ischaemia and that resulting from administration of D. C. A. (Desoxycorticosterone acetate). The renal ischaemia experiments are based upon the work of Goldblatt (1934), and implicate a humeral pressor mechanism. Wilson, (1953), has examined the renal factors. It is possible that the mechanism of renal ischaemia, with its vicious circle of hypertension and further renal damage, operates in malignant hypertension.

In studying the basophil adenomata of the pituitary, Cushing (1932), recorded observations which have been followed by the implication of pituitary and adrenal factors. Merrill (1952) has been concerned with the adrenal mechanism, suggesting a psychic origin of stress and anxiety, with resulting excess of steroids. His hypothesis is illustrated in Fig. I.

Wolferth et al, (1951), consider that the adrenal cortex is more fundamental in the maintenance of hypertension than the sympathetic nervous system. Studies upon the experimental production of hypertension will elucidate the basic aetiology of the disease, but experimentally-induced hypertension in animals fails to parallel, in many respects, the disease in man.

INCIDENCE OF HYPERTENSION IN THE ROYAL ALEXANDRA
INFIRMARY, PAISLEY: 1950 - 1953.

Medical Out-patients: During this four-year period, 4,872 persons were examined for the first time at the Out-patient Dispensaries. Of these, 841 were found to have a diastolic blood pressure of 100 mm. or over, with minimal to severe symptoms and signs of hypertension. There are several methods of ascertaining the severity of hypertension. The commonly-used classification is the four groups described by Keith et al (1938). It suffers from the limitation of being based upon the retinal changes. For the purposes of this survey, it was decided to classify the patients according to the degree to which they were incapacitated by hypertension, not taking into account the level of the blood pressure. This grouping parallels the one proposed by the New York Heart Association for the classification of disability due to lesions of the heart. Upon a clinical assessment, our patients were graded as follows:-

- I. Minimal - Those having no symptoms referable to their hypertension, or symptoms, such as headache, which produced no incapacity.
- II. Slight - Those presenting with slight dyspnoea on exertion and a tendency to early fatigue.
- III. Moderate - Those whose activity was definitely restricted by fatigue and breathlessness on exertion.
- IV. Severe - Those with severe incapacity due to hypertensive cardiovascular changes.

Fig. II shows the progressive incidence of severe incapacity in each decade of diastolic blood pressure elevation. However, the marked variation in individual response to hypertension is shown by the relatively constant incidence of moderate incapacity, which is paralleled by the frequency of slight and even minimal disability. The number of patients seen who had hypertension increased with age, the maximum being at fiftyfive years, with attenuation thereafter by death. In Fig. III. the percentage incidence of cardiac enlargement and of the symptoms, dyspnoea and fatigue, have been related to the diastolic pressure, and it will be seen that the incidence of these symptoms bears no definite relationship to the degree of hypertension present, while the incidence of cardiac enlargement demonstrated radiologically increases with the hypertension. Severe incapacity is found with an increasing frequency corresponding to the elevation

of diastolic pressure, and it is accompanied by an increasing incidence of cardiac enlargement. The incidence of the symptoms, dyspnoea and fatigue, is not related to the degree of hypertension.

Medical In-patients: There were 5,794 patients admitted for treatment during this period; of these, 564 (190 males and 374 females), were admitted on account of hypertension, their distribution in grades of incapacity being as follows:-

<u>Grade of Incapacity.</u>	<u>Males</u>		<u>Females</u>
	<u>%</u>		<u>%</u>
Minimal	10	...	10
Slight	27	...	33
Moderate	45	...	42
Severe	18	...	15

In Fig. IV. the percentage incidence of the presenting symptoms and signs is shown. Dyspnoea and fatigue are the commonest symptoms, and the figures are similar to those of cardiac enlargement. In accordance with the experience of Frant and Groen (1950), cerebral accidents were commoner in the female (27%) than in the male (18%), while congestive failure was commoner in the male (24%) than in the female (17%). Obesity was found in equal numbers of males and females under the age of forty years; it was twice as common in females in the 40 - 50 year group, and three times as common in the over-50 group. Information was obtained upon the progress of 77 per cent. of patients following discharge; 47 per cent. of males died at an average of 19

months after leaving hospital and 35 per cent of females died at an average of 23 months; cerebral vascular accidents accounted for 30 per cent. of female deaths and 19 per cent. of male deaths; heart failure was more common in the male (44%) than in the female (35%); renal failure occurred in 13 per cent. of the males and 14 per cent of the females. Of the patients admitted for treatment for hypertension, 179 were treated by ganglion-blocking agents, comprising hexamethonium and drugs of this type.

Methods of Treatment

The methods of treatment of hypertension should be related to what is known of the aetiology and the experimental production of this disease. It is essential to give consideration to the prognosis in untreated hypertension. This has been reviewed in the Lancet (1953). Leishman (1953), has suggested subdivision of non-malignant hypertension into a benign form and an accelerated form, in which deterioration is slower than occurs in malignant hypertension. The rate at which the blood pressure rises is regarded by McMichael (1952), as being more significant than the height of the blood pressure. Our clinical experience suggests that the development of symptoms and signs appears to be mainly due to the ability, or otherwise, of the individual patient's cardiovascular system to sustain the load of the hypertension. High levels of diastolic pressure are compatible with slight or even minimal

incapacity in the individual. In essential hypertension, it is probable that elevation of diastolic pressure is compatible with a reasonable prognosis, except when signs and symptoms of heart failure appear. Headache, as Stewart, (1953) has found, is a symptom which is probably unrelated to the severity of the hypertension. Renal involvement and cerebral vascular disasters occur, as a rule, late in the disease, and are not amenable to other than palliative treatment. While the onset of heart failure constitutes a cardinal indication of the need for active therapy, the factors leading to the hypertension itself require study. A rise in the systolic pressure accompanied by a moderate elevation of the diastolic pressure of the order of 10 to 20 mm. tends to occur as the arteries harden with age. To some extent this finding has biased observations upon the prognosis of hypertension. The studies which have been performed are of relatively short duration, and systematic observation over a long period is required. Acceptance as physiological of an increasing diastolic blood pressure with advancing age is probably unjustifiable, in that Kean and Hammill (1949) have shown that among primitive peoples this does not occur, hypertension being associated with stresses encountered in civilised life. Graham (1945) has noted that, under the stress of prolonged periods of desert warfare, transient rises of pressure occurred, and Gavey (1954), suggests that, under conditions of long-continued stress, the hypertension may become fixed. Wolf et al (1948) and Gressel et al (1949),

have indicated that hypertensive vascular disease may be associated with obsessive compulsive traits and subnormal assertiveness, leading to an attitude of restrained aggression to the threats and challenges of everyday life, the vascular component of which comprises an elevation in the blood pressure and renal vasoconstriction. The study by Platt (1947) has confirmed that there is a marked hereditary predisposition. Implication of a stress mechanism is strongly suggestive of a close parallel with the D. C. A. -induced hypertension in the animal, and with the hypertension of Cushing's syndrome. In recent years, this has led to attempts to control hypertension by adrenalectomy. The results of this operation have been unsatisfying, and it is often combined with subtotal sympathectomy. Bowers (1954) has suggested that sub-total adrenalectomy should be restricted to malignant hypertension which cannot be controlled by medical therapy, chronic hypertension with marked organic changes, and Cushing's syndrome. Jeffers et al (1953) performed a total or sub-total adrenalectomy with a modified Adson type of sympathectomy in the treatment of 99 patients with severe hypertension. In 23% the response was excellent; in a further 23%, a fair response was obtained; the response was poor in 30%, and 24% died post-operatively. The indications for adrenalectomy are therefore limited. A less active approach on the adrenal mechanism is made by restriction of dietary sodium intake, and to this the Kempner (1948) rice-fruit-sugar diet owed part of its success.

Schroeder et al (1939) have concluded that the rice diet itself is of questionable value, but it is low in protein and very low in salt content; furthermore, it had a strong psychotherapeutic influence. The value of a diet containing sodium chloride in low daily intake of 0.5 to 2 g. is demonstrable, and its combination with a low calorie intake is desirable. Martin (1952) has shown that reduction in obesity does not produce a significant fall in the diastolic blood pressure, but Fishberg (1937) has stated that reduction in dietary intake is followed after a week or two by a fall in the basal metabolic rate, and maintenance of this at a lower level reduces the load upon the heart to an extent which permits of an adequate control of the signs and symptoms of many patients with moderate elevation of the diastolic pressure. The milk diet introduced by Karell (1866) is initially very useful, and after a period of 72 - 96 hours, this can be followed by an 800-calorie diet, the sodium content of which should be under 2 g. Reducing diets of this type are specially indicated in the obese, and they are of value in all cases of hypertensive heart failure.

Relief of stress is an important part of treatment, but in many cases it may be impractical to prescribe an alteration in the patient's activities or environment. Where hypertensive incapacity is severe, bed-rest is essential. It is necessary to relieve any degree of anxiety from which the patient may suffer, and sedation will depress the psychic stimuli which Merrill (1952) has implicated. In Out-patients, phenobarbitone in dosage of up to g. 1 thrice daily, can be

prescribed, and for In-patients, we have used sodium amytal in dosage of up to gr. 3. thrice daily.

A further factor of potential importance in the treatment of hypertension is the occasional occurrence of primary renal disease, due to chronic infection or to renal anomaly. Unilateral renal disease has not been encountered during our survey, and although Pickering and Heptinstall (1953) have recorded successful results following nephrectomy, Smith (1948), has concluded that nephrectomy should be restricted to the relief of definite unilateral renal disease amenable to operation, and not performed with hypertension as the indication. In advanced hypertension, nephrectomy may actually shorten life by reducing still further the remaining functional renal tissue.

In summary: the general measures of treatment consist of relief of stress due to anxiety and environment, using sedation to assist in this, and treatment of heart failure by rest and restricted-sodium, low-calorie diets.

REDUCTION IN THE LEVEL OF BLOOD PRESSURE

The general methods of treatment are directed to modification of the circumstances which have occasioned the hypertension, and reduction of the load placed upon the heart. In that the cardiovascular changes are due to the elevated blood pressure, there is an obvious necessity to use the means at our disposal to lower this. White (1947) lists many of the preparations previously used.

I. SYNTHETIC GANGLION-BLOCKING AGENTS

(a) Hexamethonium: During a search for synthetic curarising agents, Paton and Zaimis (1949), found that the sixth member of the methonium series of compounds (hexamethonium) possessed a marked and selective action in blocking the ganglionic synapse of the autonomic nervous system, and Arnold and Rosenheim (1949) demonstrated that the relaxation of sympathetic tone which is produced by this drug in man is followed by arteriolar dilation, with reduction in the peripheral resistance. This occasions a marked fall in the blood pressure in both normotensive and hypertensive patients. Hexamethonium has been used extensively to decrease the blood pressure of patients with signs and symptoms of hypertension, and the results of treatment have been reviewed by ourselves with Campbell (1952), by Shaw (1952), and by many others.

(b) Pentapyrrolidinium. (Ansolyzen - M & B 2050) One of us with Campbell (1953), has described a search for improved synthetic drugs, which resulted in the selection of a homologue of hexamethonium, pentapyrrolidinium, as offering some advantages over hexamethonium. Smirk (1953a) has confirmed these findings.

Hexamethonium, its homologues and compounds of this type are characterised by their ability to produce an immediate and usually marked fall in the blood pressure, the extent of which is dependent upon the dosage used and the individual degree of susceptibility of the patient. Side actions occasioned by unselective ganglionic

blockage are to be expected, and consist of constipation, dryness of the mouth and blurring of vision. Tolerance develops quickly, so that dosage has to be increased to a maintenance level. The degree of control of the blood pressure attained varies from patient to patient, and oral dosage is useful in a proportion of patients only, since absorption from the gut tends to be variable.

II. 1-HYDRAZINOPHTHALAZINE (Apresoline - Ciba) This drug is said to have a central action upon the hypothalamus, and produces peripheral vasodilation by a partial blocking action of adrenaline and nor-adrenaline. Its action has been studied by Schroeder (1952), Hafkenschiel and Lindauer (1953) and others. The action of 1-Hydrazinophthalazine is slower than that of hexamethonium, and, as its sites of action are different from those of the latter drug, combination of the two has been found to be of value. As has been reported by Schroeder (1952a), the side actions are tachycardia, headache, vertigo, and nausea and vomiting. They tend to be transient as treatment is continued.

In limited experience, we have not been impressed by the activity of 1-Hydrazinophthalazine in comparison with that of hexamethonium, and have not therefore used this drug in treatment.

III. VERATRUM ALKALOIDS The alkaloids of veratrum veride produce a fall in the blood pressure which is probably due to a central action, and is accompanied by a bradycardia due to stimulation of peripheral vagal nerve-endings. Wilkins et al (1949) and others have used

this drug in the treatment of hypertension. It is available in this country as Veriloid - Riker. Mills and Moyer (1952) have found that the hypotensive dose closely approximates to the toxic dose which produces vomiting. They noted that this prevents effective use in the therapy of hypertension, and they prefer hexamethonium.

IV. HYDROGENATED ALKALOIDS OF ERGOT: In contrast to the natural alkaloids or ergot which cause contraction of smooth musculature and vasoconstriction, certain di-hydrogenated alkaloids occasion peripheral vasodilation and block adrenergic stimuli. This has been described by Rothlin and Cerletti (1949). They are available in this country as Hydergine - Sandoz. The action of these alkaloids in the control of hypertension described in the literature is unpromising, and limited personal experience has tended to confirm this.

V. RAUWOLFIA SERPENTINA: An alkaloid was extracted from this tropical shrub by Muller et al (1952). Its action is said to be central, and it tends to produce a subjective improvement. The effect on the blood pressure is minimal, but it is free from side actions. It is possible that it may be useful as an adjuvant to more active forms of therapy. The pure alkaloid is available as Serpasil - Ciba. Its is combined with Veratrum alkaloids in the preparation of Rauwiloid - Riker. It is probable that it will be used in combination with hexamethonium. Wilkins et al (1954) have reported favourably on this drug.

INDICATIONS FOR TREATMENT

Group I: In view of the favourable prognosis in asymptomatic benign hypertension, no active therapy appeared to be indicated in the majority of those patients. A few patients presented with pressures over 120 mm. below the age of 40 years, and over 140, and lowering of such pressure levels was attempted, together with close observation.

Group II: Slight breathlessness on exertion and a tendency to early fatigue responded well to reassurance and sedation, with some restriction of activity.

Groups III and IV: Moderate and severe incapacity required active treatment in hospital with the general measures outlined earlier. Of the patients in these groups, one hundred and forty-nine were treated, in addition, with methonium compounds. The total of one hundred and seventy-nine patients treated with methonium compounds includes those in the first group and fourteen cases of malignant hypertension noted subsequently.

There were two indications for the use of methonium compounds:

(1) The presence of moderate or severe incapacity, and failure of the pressure to fall below 100 mm. within a fortnight or more in response to general measures of treatment. The range of initial pressure levels varied widely in the groups, as hypertension tends to be reduced when failure occurs. In the moderate cases, the pressure was frequently labile, responding well to rest and sedation during the first admission,

but within months or years, the hypertension became fixed, so that subsequently methoniums became indicated.

(2) High levels of pressure, usually in excess of 140 mm, accompanied by acute complications such as blindness, encephalopathy and heart failure, constituted an indication for immediate dosage with methonium compounds.

RESPONSE TO TREATMENT

Severe symptoms and signs of hypertension were improved by reduction in the blood pressure, and, with Campbell (1952), we have analysed the results obtained with methonium therapy. Similar results have been recorded by many others. While it is possible to effect reduction to normal pressure levels in almost every In-patient, subsequent observation generally shows a rise of pressure approaching the untreated level. However, it has often been observed that a fall occurs if the patient is again admitted, or is adequately rested. Methonium therapy tends to restore the lability of diastolic pressure.

In 60% of the patients, intermittent oral dosage with hexamethonium bitartrate in amounts totalling 0.75 G. to 2 G. of cation per day, has been adequate to control signs and symptoms; a further proportion have required parenteral injection of this drug in quantities of up to 300 mg. of cation per day. In common with Smirk (1954) we have not been able to ascertain whether treatment has extended the life expectation, but during the period of survival, restoration to activity approaching normal

has often been achieved. Pentapyrrolidinium has provided a more certain method of lowering the blood pressure. Total dosage of up to 150 mg. of cation parenterally has been applied, and 1000 mg. orally, in some cases. The retard preparation described by Smirk (1953b), has been found valuable in reducing the number of injections necessary to one or two per day. During treatment with hexamethonium, wide variations in pressure are often recorded, with fluctuations due to emotion. The pressure levels during pentapyrrolidinium therapy are more stable. This is probably due to the greater effect of this drug upon the sympathetic nervous system than the parasympathetic. Pentapyrrolidinium has proved much more certain in action, and in no case has a significant fall in blood pressure failed to occur following adequate dosage.

MALIGNANT HYPERTENSION

Fourteen patients presented with malignant hypertension; in seven there were no signs or history of previous hypertension; the others had hypertension of long standing, which had entered into a malignant phase.

Malignant Hypertension of Recent Origin: Three patients had chronic nephritis, and when first observed, had gross impairment of renal function, with uraemia. Four patients had no previous history of renal disease, renal function was good and blood urea was low during initial investigation, suggesting a diagnosis of primary malignant hypertension. Impairment of vision was a frequent symptom. Examination of the fundi showed fresh haemorrhages and woolly exudates with frank papilloedema.

No cardiac enlargement was present. The average diastolic pressure level was 140 mm. The duration of life was greater in those with chronic nephritis, extending from 12 days to four years, than in those with primary malignant hypertension, who died in from eight to nineteen months. Uraemia was progressive in all cases, as was a severe hypochromic anaemia.

Malignant Phase of Hypertension: This occurred in older patients who had a history of hypertension of at least several years' duration. Impairment of vision was less commonly complained of, the presenting features being breathlessness on exertion and fatigue. Cardiac enlargement was present in all cases. The blood urea was either normal or but little raised, except terminally in one patient. Anaemia did not occur. Fundal examination showed sclerotic changes in the retinal arteries, old waxy hyaline exudates, and chronic retinal and disc oedema; fresh haemorrhages and exudates were superimposed. The prognosis was much better in this than in the previous group, five of the seven patients being alive after eight months to four years. One female died from a cerebral haemorrhage, and one male from uraemia.

As is described by Hadfield and Garrod (1947), a sudden rise in blood pressure causes arteriolar necrosis, in contrast to the fibrous thickening in the vessel walls which occurs in essential hypertension. In the first group, extensive arteriolar damage occurred, particularly in the retina and the kidney. In the second group, the arterioles were thickened to withstand chronic hypertension, and the subsequent changes were less severe.

Ganglion-blocking agents produced a fall in pressure to normal levels, with a dramatic improvement in the symptoms and signs in the twelve cases treated. Effective control of the pressure was not obtained after discharge of these patients from hospital, due to causes such as postural hypotension, constipation, vomiting and diarrhoea, blurring of vision, and in some instances, discontinuance by the patients themselves of therapy. Even when full dosage was used, the natural tendency of the patient to return to normal activity was followed by a rise in the pressure level. In the later stages, control in hospital of the pressure level failed to arrest deterioration. However, regression of symptoms and signs of the malignant phase of hypertension was obtained more readily, with a probable extension of life.

DISCUSSION

The marked improvement in the symptoms and signs in patients with hypertension which follows the application of general measures of treatment with and without ganglion blocking agents has led us to adopt the hypothesis that control of the pressure level will return those patients to the category of asymptomatic hypertension, the prognosis of which is good. It has appeared reasonable to adopt measures which produce only a moderate reduction in the diastolic pressure level, as, from observation, the actual level is of less importance than the individual response to it. The period of

observation has been inadequate to decide whether this symptomatic approach to treatment has increased, or has failed to extend the expectation of life. However, observation of a few patients with hypertension in acute form, malignant hypertension, suggests that maintenance of the blood pressure at a level approaching normal, e.g. under 100 mm., is probably desirable in a proportion of individuals if the life expectation is to be increased. We have found that a marked reduction is not well tolerated by patients who have been accustomed to hypertension of several years' duration. Schroeder (1952b), has observed that this period of discomfort and loss of energy is transient, adaptation to the lower level gradually taking place.

If it is agreed that reduction in the level of the diastolic pressure is desirable, ganglion blocking agents are the drugs of choice, in that they alone produce an immediate and definite fall in pressure. Maintenance of this effect is difficult to accomplish, owing to the development of tolerance to the drug, and is comparable with the regression following sympathectomy. It might be advisable to combine ganglion blocking agents with other drugs which have different sites of action. A simple homologue of hexamethonium, pentapyrrolidinium, has been found to be more useful in that it is more predictable in action, and duration of action is longer, and more stable control is obtained. It is probable that further work in the development of ganglion blocking agents will result in the discovery of new compounds of greater value. Whatever the initiating mechanism of hypertension, the factor

responsible for its maintenance is the arteriolar tonus, as has been shown by the response to sympathetic block. Treatment with ganglion blocking agents must be considered to be symptomatic, in that no permanent alteration in the pressure level is achieved, and a rise always follows withdrawal of drug dosage. It is possible that at some future date, advancement in knowledge of the synthesis and metabolism of cortical steroids may result in the production of compounds which will inhibit these, and will permit of a more fundamental control of hypertension. Alternatively, in that constriction of the arterioles is a function of nor-adrenaline, it is possible that means will be found to increase the activity of the enzyme iminase, which is responsible for the destruction of this pressor amine.

SUMMARY

Although the prognosis in uncomplicated hypertension is usually good, elevation of the diastolic blood pressure is in many cases followed by symptoms and signs of heart failure, and when these develop, the expectation of life is limited. General measures of treatment are rest, sedation, a salt-poor diet, and subsequent restriction of mental and physical activity. If these prove inadequate, and if the blood pressure is not labile, methonium compounds are indicated.

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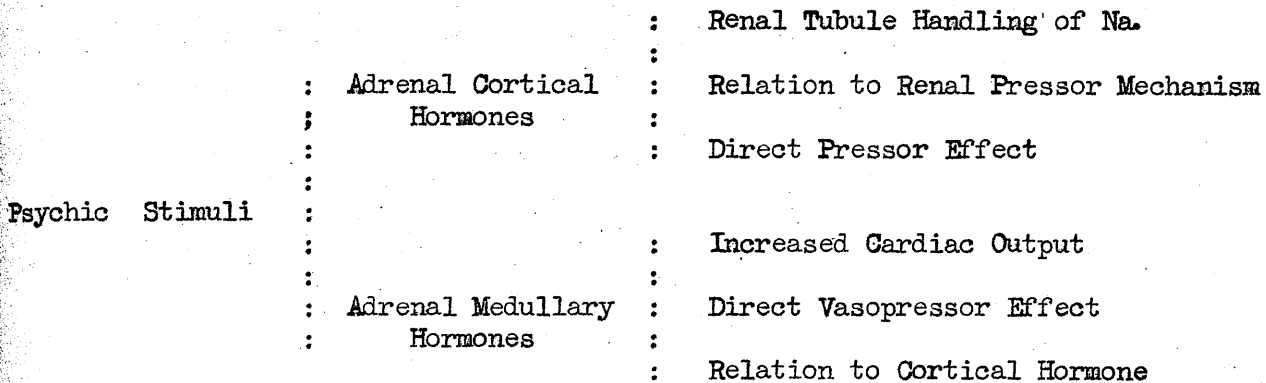


Fig. I

Psychomotor mechanism of hypertension, (after Merrill).

SYMPTOMS	MALE	FEMALE
Dyspnoea and Fatigue	71	81
Headache	30	51
Chest Pain	12	13
SIGNS		
Cardiac Enlargement	73	82
Cerebral Accident	18	27
Congestive Failure	24	17
E. C. G. L. V. P.	54	58
Fundi Grade II and III	87	83

Fig. IV.

Percentage incidence of symptoms and signs in
patients admitted for treatment of hypertension.

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NEW SYMPATHICOLYTIC AGENTS

R. D. H. MAXWELL

M.B., B.Sc. Glasg.

CLINICAL ASSISTANT, ROYAL ALEXANDRA INFIRMARY, PAISLEY ;
MEDICAL ADVISER TO NEW PRODUCTS DIVISION,
MAY & BAKER LTD.

A. J. M. CAMPBELL

M.B. Glasg., F.R.F.P.S.

MEDICAL REGISTRAR, ROYAL ALEXANDRA INFIRMARY,
PAISLEY

SINCE the indication by Paton and Zaimis (1948) that the ganglion-blocking action of compounds of the methonium series would have a clinical application, many reports have been published on their use in hypertension. These have been reviewed (*Lancet* 1951, *British Medical Journal* 1951, Turner 1951), and enough time has now elapsed to suggest that with hexamethonium it is possible to modify in some cases the course and prognosis of hypertension with severe symptoms and signs. Campbell et al. (1952), Grimson (1952), and others have reported results of treatment lasting two years or more. It can be concluded that, although hexamethonium has no action on the cause of hypertension, it can modify the hypertension of some patients, giving a variable degree of relief from symptoms and signs.

Meanwhile the search for other hypotensive agents has continued. Study of the actions of the hydrogenated alkaloids of ergot (Rothlin and Cerletti 1949 and others) has been extended. Baikie and Smith (1952) and Smirk (1952b) have examined 'Pendiomide.' Apresoline and regitine have been used by Grimson (1952).

Hexamethonium is not an ideal drug for the production of sympathicolysis in the treatment of hypertension.

(1) It produces a generalised ganglion blockade affecting gastro-intestinal activity (Kay and Smith 1950), which may lead to paralytic ileus (Mackey and Shaw 1951, and others). Other actions include inhibition of salivation, paralysis of ocular accommodation, and reduction of sweating, the last having been used in the treatment of hyperhidrosis by Sommerville and McMillan (1952).

(2) It is inconstant in action, there being also an individual variation of response. This variation is increased when hexamethonium is given by mouth. Further, a strong tolerance develops rapidly, making large doses necessary for continuous treatment.

(3) The duration of action of a dose of hexamethonium is normally short, making frequent injections necessary when it is given parenterally. Masini and Rossi (1952) and Smirk (1952a) have used macromolecular substances, such as polyvinylpyrrolidone and dextran, to provide depot injections of hexamethonium salts and thus to prolong their action.

Paton (1951) suggested that it might be possible to obtain ganglion-blocking agents exerting selective action on different parts of the autonomic nervous system. With Graham, we have described results with 'M. & B. 1863' or 'Gaplegin,' a monoethyl homologue of hexamethonium which we found to be of greater activity but without any great specificity of action (Campbell et al. 1952). Smirk (1952b) has confirmed these findings.

Wien and Mason (1953) have examined new compounds prepared by May & Baker Ltd., some of which possess strong ganglion-blocking activity. In view of the known species difference in response to these drugs, we selected nine of them for examination of their actions in man in comparison with hexamethonium and gaplegin.

The new compounds examined are structurally related to hexamethonium. They are:

M. & B. 2074. Butane-1 : 4-bis(diethylmethylammonium hydrogen tartrate) dihydrate.

M. & B. 1950. Phenylethane-p- ω -bis(trimethylammonium dihydrogen phosphate) tetrahydrate.

M. & B. 2034. N,N'-tetramethyl- β -p-aminophenylpropylamine bismethobromide.

M. & B. 2002. Pentamethylene-1 : 5-bis-4'-(4'-methylmorpholinium) dibromide.

M. & B. 1978. Hexamethylene-1 : 6-bis-4'-(4'-methylmorpholinium) di-iodide.

M. & B. 2023. Heptamethylene-1 : 7-bis-4'-(4'-methylmorpholinium) dibromide.

M. & B. 2050A. Pentamethylene-1 : 5-bis(1'-methylpyrrolidinium) bitartrate.

M. & B. 2024. Hexamethylene-1 : 6-bis-N-(N-methylpyrrolidinium) di-iodide.

M. & B. 2060. Hexamethylene-1 : 6-bis-N-(N-ethylpyrrolidinium) dibromide.

Dosage of these we have expressed in terms of active cation.

METHODS

Grimson et al. (1952) and others have noted that the response of hypertensive patients to the initial dose of hexamethonium may be excessive. Accordingly we decided to investigate the action of drugs with strong hypotensive properties first in patients with normal blood-pressures and subsequently in patients with hypertension, a procedure similar to that of Arnold and Rosenheim (1949) when they examined hexamethonium. As a record of the effect on the gastric secretion was required, which involved repeated swallowing and toler-

ance of Ryle's tubes, 75 patients with duodenal ulceration and hyperchlorhydria without cardiovascular abnormality were selected. Subcutaneous administration was begun with 2.5-5 mg. of cation repeated at short intervals in increasing dosage until a definite effect was observed. To minimise errors due to tolerance or to variations in sensitivity, the same drug was not given again to any patient and the drugs were given in different order. The smallest number of observations made on any drug was ten, but more observations were made on those found to be of interest. Control experiments with injections of sterile water were made in each patient. The effects on the blood-pressure, pulse-rate, and pupil size were determined. Change in skin-temperatures indicated alteration in peripheral circulation, and change in skin resistance indicated alteration in the activity of the sweat-glands. Paralysis of visual accommodation (shown by inability to read) and dryness of the mouth were noted. With the patient fasting the gastric secretion was aspirated completely an hour before, and again shortly before, the drug was given and hourly thereafter.

Exact techniques were considered to be less important than identical methods of comparison of each drug with adequate control. Once the active drugs were identified, observations were repeated to confirm the results obtained; 328 doses were given during this part of the investigation. Subsequently the two most active sym-

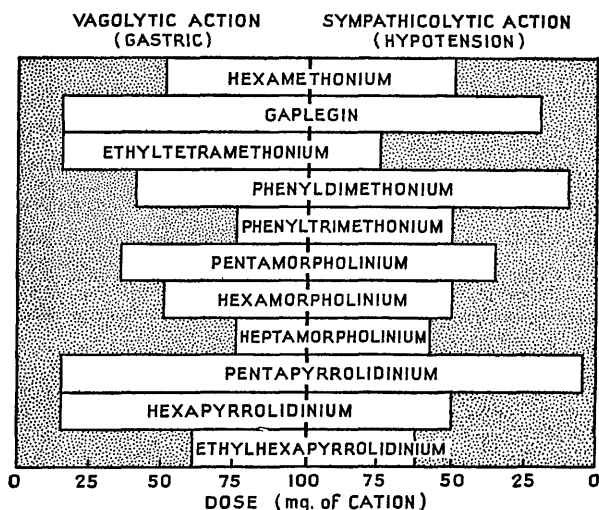


Fig. 1.—Comparison of vagolytic actions on gastric secretion and sympathicolytic (hypotensive) actions of hexamethonium, gaplegin, and nine new sympathicolytic agents.

patholytic drugs were administered to hypertensive patients, and their effects on the blood-pressure and their side-effects were studied.

CLINICAL RESULTS

From the results it was possible to estimate the dose of cation which, injected subcutaneously, would definitely lower the blood-pressure of hypertensive patients, and the dose which would produce achlorhydria in the fasting secretion of patients with hyperchlorhydria, in at least 60% of first observations. These results are comparable with the actions of hexamethonium in subcutaneous initial doses of 50 mg. of cation.

The distribution of the activity of these drugs in comparison with hexamethonium and gaplegin is shown in fig. 1. Their action in producing mydriasis and an alteration in peripheral circulation when used in hypotensive dosage is shown in fig. 2. The effect of these compounds on the heart-rate was similar to that of hexamethonium, a variable production of tachycardia during hypotension. Paralysis of visual accommodation and dryness of the mouth were in keeping with the mydriasis recorded. The effect on sweating was less than that of hexamethonium in the dosage used. No drug affected the respiration-rate or showed any sign of curarising activity.

Fig. 1 shows that M. & B. 1950 (phenyldimethonium) and M. & B. 2050 (pentapyrrolidinium) have the highest

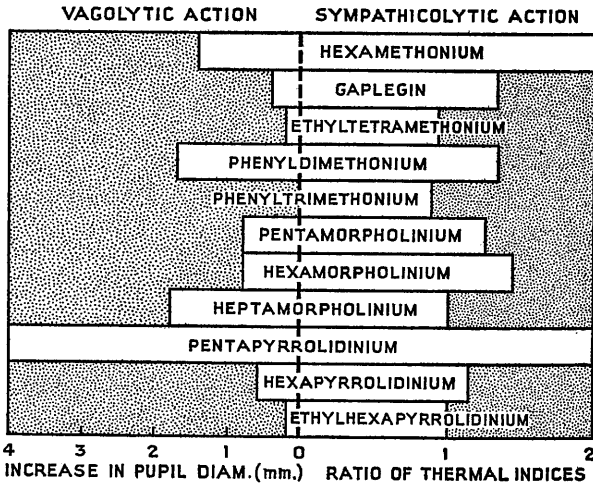


Fig. 2.—Comparison of vagolytic actions on pupil size and sympathicolytic actions on thermal indices of hexamethonium gaplegin, and nine new sympathicolytic agents.

CHARACTERISTICS OF PHENYLDIMETHONIUM AND PENTAPYRROLIDIUM COMPARED
WITH THOSE OF HEXAMETHONIUM IN SINGLE DOSES

Drug	Minimal effective dose (mg.)		Duration of action (hr.)		Consistency of action		Gastric activity	Mydriasis
	Subcutaneous	Oral	Subcutaneous	Oral	Subcutaneous	Oral		
Hexamethonium ..	50·0	500 +	2-4	?	+++	+	+++	+
Phenyldimethonium ..	5·0-15·0	25-100	6 +	8 +	+++	++	+	++
Pentapyrrolidinium ..	2·5-10·0	25-100	6 +	8 +	+++	++	++	+++

sympatholytic activity. Phenylmethonium has a relatively selective action in depressing the blood-pressure, and pentapyrrolidinium is the most active of the drugs used, having also a high generalised activity. The effects of these two drugs were investigated in 15 patients with hypertension, of whom 10 had previously been treated with parenteral and oral hexamethonium. The effect of single doses was studied first, in comparison with hexamethonium and control doses of sterile water, with intervals of several days between doses to avoid habituation. Fifty subcutaneous doses of each drug were given, varying between 2.5 and 50 mg., and subsequently the effects of fifty oral doses of 25-150 mg. of each were recorded. The results are presented in the accompanying table.

These two drugs produce hypotension when given subcutaneously in a dosage which is from a tenth to a fifth of the amount of hexamethonium required to produce a comparable fall in blood-pressure. Pentapyrrolidinium is the more active of the two. The hypotension lasted from six to thirty-six hours, excluding the period of recovery of blood-pressure. Hexamethonium in single oral doses of 500 mg. does not produce hypotension consistently, but single oral doses of these new drugs produced hypotension in 56% of the observations made. Hypotension appeared two to four hours after oral dosage and lasted for eight hours or more. Both drugs produced side-effects in excess of those which followed doses of hexamethonium. Pentapyrrolidinium almost invariably produced mydriasis and dryness of the mouth, and occasionally headaches with drowsiness and depression. Little difference in their activity was noticed when they were administered to patients who were tolerant to hexamethonium.

In subsequent continuous treatment with phenylmethonium and pentapyrrolidinium in divided subcutaneous doses totalling 50-100 mg. daily and divided oral doses totalling 100-150 mg. daily, results comparable with our previous experience with hexamethonium were obtained. The side-effects previously met with tended to persist, but constipation was not troublesome.

Severe Hypotension

The application of the new drugs of high activity produced severe hypotension on several occasions. Blood-pressure levels of 80/50 mm. Hg in the recumbent position were well tolerated by normotensive patients, who lost consciousness only if they stood up. Hexamethonium produced a rapid symptomless postural faint with moderate tachycardia and a warm skin. The postural faint with pentapyrrolidinium was very different. It was preceded by nausea and often vomiting. Loss of consciousness was slow and accompanied by tachycardia

and pallid cold sweating. The effects of phenyldimethonium were intermediate between those of hexamethonium and those of pentapyrrolidinium.

Severe hypotension was not well tolerated by hypertensive patients. Electrocardiography revealed almost constant changes affecting the ST segment and T waves, which may also be seen in normotensive patients. Hypotensive measures are likely to be dangerous in the presence of coronary arterial disease. No treatment of the severe hypotension is necessary other than rest in bed with the feet raised until the drug's action ends, adrenaline being contra-indicated (Burn 1951).

DISCUSSION

These results indicate that phenyldimethonium and pentapyrrolidinium probably overcome some of the disadvantages of hexamethonium. As regards selectivity of action, their doses which produce hypotension are smaller than those required to affect gastric secretion. Kay and Smith (1950) have shown that the paralysis of vagal ganglia by hexamethonium in hypotensive dosage inhibits the volume and acidity of gastric secretion in hyperchlorhydric patients. Gastric motility is difficult to study, because the concomitant severe hypotension often causes nausea and vomiting, but it is improbable that inhibition of gastric motility can be produced by ganglion-blocking agents in the absence of an action on gastric secretion.

Preliminary observations suggest that constipation is less during continuous oral treatment with these drugs than with hexamethonium, indicating a smaller risk of paralytic ileus. Inhibition of sweating is less, and the incidence of dryness of the mouth is about the same, but mydriasis is more common and more severe with both of the new drugs, and pentapyrrolidinium has been observed to produce sustained mydriasis during continuous treatment.

Both drugs are more consistent in action than hexamethonium when used orally, and single oral doses produce a definite hypotension more often, although comparably with hexamethonium the hypotensive effect may be delayed until several doses have been given. Habituation develops at least equally rapidly—probably more rapidly with pentapyrrolidinium—but a satisfactory reduction of blood-pressure is often obtainable with a daily dosage very much smaller than that of hexamethonium.

The two drugs appear to be effective even after habituation to hexamethonium, and may be sometimes used successfully by mouth in patients who have not responded to oral hexamethonium. The duration of response in parenteral administration is longer, suggesting

that frequency of dosage may be reduced compared with hexamethonium; but in continuous parenteral treatment we have found that at least three doses a day are required.

Headache, drowsiness, and depression are unusual side-effects of pentapyrrolidinium, but their incidence and severity have not been such as to necessitate withdrawal of this drug. The high activity of these new drugs requires caution in their administration to avoid severe hypotension.

Fig. 1 shows that M. & B. 2074 (ethyltetramethonium) and M. & B. 2024 (hexapyrrolidinium) act on gastric secretion in a dosage not affecting blood-pressure. Studies of the application of these drugs in the management of hyperchlorhydria are in progress.

SUMMARY

Examination of nine new ganglion-blocking agents has indicated that two of them, phenyldimethonium and pentapyrrolidinium, have a high degree of activity in man in reducing the blood-pressure.

Pentapyrrolidinium is the more active of the two but is less selective in action.

Their action lasts longer than that of hexamethonium, and more consistent results follow oral dosage.

The preliminary results suggest their suitability for examination as therapeutic drugs in the management of hypertension.

We are grateful to Dr. J. Gibson Graham for permission to make this investigation and for his advice and encouragement; to the nurses of this hospital for their coöperation in managing the patients; and Miss K. J. S. Brander for laboratory and documentary assistance. The drugs were supplied by Messrs. May & Baker.

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DISEASES OF THE CARDIOVASCULAR SYSTEM¹

BY J. GIBSON GRAHAM AND R. D. H. MAXWELL
The Royal Alexandra Infirmary, Paisley, Scotland

CORONARY ARTERIAL DISEASE

Exogenous cholesterol metabolism in man has been studied by Biggs *et al.* (1) using tritium-labeled cholesterol. Ingested cholesterol was demonstrated in an atherosclerotic aorta. Severe hypercholesterolemia was produced in rats by Page & Brown (2), intimal lipid infiltration occurring but atherosclerosis failed to develop. A sustained low blood cholesterol level has been obtained in man by Pollak (3) using sitosterol in oral dosage of 5 to 10 gm. per day. Paterson (4) considers the precipitating factor in coronary artery occlusion of capillary rupture within the atherosclerotic plaques is more important than the degree of atherosclerosis.

The early assessment of coronary artery insufficiency is of importance. Master *et al.* (5) give criteria of electrocardiographic changes following their exercise test which they consider to be more significant than the resting electrocardiogram. Ischemic electrocardiographic changes comparable with those following exercise have been demonstrated by Contro *et al.* (6) after amyl nitrite inhalation, and the use of this as a simple functional test is suggested.

Attention has been drawn by Papp & Smith (7) to the clinical entity of slight cardiac infarction. Cardiac pain, angina of effort, and a variable degree of shock and failure occur, but laboratory and clinical signs are minimal. The pathological lesions correspond to small areas of infarction which represent the acute stage of patchy myocardial sclerosis resulting from arteriosclerotic narrowing of the main coronary arteries and not from a local arterial occlusion. Clinical recovery occurs in a high proportion of these cases. Q waves were absent in one-half of this group of patients and R-T changes were of the subacute type. Changes were found mainly in leads III R and aVFr, exercise being useful in demonstrating ischemia. Severe cases of posterior infarction had a mortality of 33 per cent; the prognosis in the moderate group was good. Elek *et al.* (8) have found the left back leads of value in diagnosis.

High posterolateral infarction of the anatomical left surface of the heart has been the subject of an interesting study by Tulloch (9). Diagnostic signs of infarction are found in VL and lead 1. A predominant R wave is found in V1, with absence of a definite transitional zone in the precordial leads, a high upright T wave in two or more of these, and in the acute stage, S-T depression. Additional back leads are useful.

Electrocardiographic and pathologic changes following infarction of the

¹ The survey of literature pertaining to this review covers the period from July, 1952 to June, 1953.

interventricular septum have been correlated by Osher & Wolff (10). Septal lesions were always associated with infarction of the free wall anteriorly or posteriorly, both walls being usually involved. Massive septal infarction is probably usually fatal, but septal involvement of significant degree is common in myocardial infarction. A diagnosis of septal infarction can be made when conduction defects appear during the course of acute myocardial infarction, and in their absence the appearance of QS deflections with abnormally elevated S-T segments in right precordial leads is strongly suggestive of septal involvement.

Methods of diagnosis of myocardial infarction in the presence of anomalous conduction have been suggested by Wolff & Richman (11).

Brigden & Shillingford (12) in their examination of vectorcardiograms have found constant deviation of the loop from the site of infarction which is demonstrated best in the horizontal plane in anterior, and the frontal plane in posterior infarctions. The ballistocardiogram was found to be more sensitive than the electrocardiogram by Scarborough *et al.* (13) in the detection of coronary artery insufficiency, but its diagnostic significance was impaired by the frequency of ballistic abnormality in normal subjects, which increases with age. It is suggested that significance be attached to abnormal ballistocardiograms from subjects under the age of 50 and to normal ballistocardiograms from those over the age of 60.

The mortality rate of patients with shock following myocardial infarction was found by Selzer (14) to be more than twice that of patients without shock. Four categories were evident: immediate mild shock, immediate fatal shock, delayed shocklike state associated with arrhythmias, and delayed shocklike state with fatal cardiac failure. It is suggested that early shock may be initiated by a vasomotor mechanism, but the last group is a result of irreversible cardiac failure of the forward type. Selzer (15), using dogs, has described a method by which the competence of the heart can be estimated by response of the intraventricular pressure to a standardized stimulus overloading the left ventricle by increasing the peripheral resistance. It was necessary to ligate two major branches of the coronary artery thereby producing a massive myocardial infarction before cardiogenic shock was reproduced.

The necessity for immediate and vigorous treatment of shock following acute myocardial infarction is emphasised by Goodnick & Knox (16), who record improvement in survival following treatment with vasopressor drugs and blood or plasma. An untreated mortality of 80 per cent was the experience of Hellerstein *et al.* (17) who have found mephentermine produced a satisfactory pressor response which did not produce or aggravate congestive failure.

An extensive review of the mechanisms involved in blood clotting has been prepared by Wright (18) together with a survey of the methods of preventing or protracting this. Attention is drawn to the complexity of the process, its unpredictability, and lack of a certain relationship between the clotting time of the sample of peripheral venous blood withdrawn and the

clotting time elsewhere in circulation. A new factor, serum accelerator-globulin, is mentioned, and its physico-chemical involvement is examined. It is suggested that heparin and other anticoagulants, by increasing the negative zeta potential of the vessel wall, inhibit initial clotting stages by increasing a tendency to repel blood components with possible lessening of the platelet adhesiveness. Blood stasis with sludging is an important feature in patients confined to bed. Of the anticoagulants used, ethyl biscoumacetate (Tromexan) remains the most useful. Rosenthal & Weaver (19) have found that the heparin clotting time, which provides an indication of over-all coagulability, was accelerated in 74 per cent of patients with acute myocardial infarction examined within three weeks after the attack. Peel (20) has used Rosenthal's heparin-retarded coagulation time as a method of selection of patients with coronary artery disease for anticoagulant therapy, suggesting that thereby it can be concentrated upon those patients most in need of it.

Further experience has mainly confirmed the value of anticoagulants in myocardial infarction. Loudon *et al.* (21) have recorded a mortality of 41 per cent in the control group and 25 per cent in the treated group. Griffith *et al.* (22) experienced a significant reduction in thromboembolic complications. Scarbrone *et al.* (23) have confirmed the general advantages of anticoagulant therapy. The employment of anticoagulants is considered by Gilchrist (24) to be an outstanding contribution to the treatment of myocardial infarction, and he states that by their efficient use the death rate over the first six weeks can be halved and the dangers of thromboembolic complications be reduced to negligible proportions while they have in addition a favourable influence on the outcome of the shock syndrome. The need for prompt reversal of the shock mechanism and the methods available have been noted. However, Feldman *et al.* (25) found that anticoagulant therapy had no influence upon the mortality of their series of patients. Further to this, Schnur (26) has critically examined the progress of 1350 patients with acute myocardial infarction admitted over a 10 year period, and he has surveyed the literature critically. He states unequivocally that there is no convincing evidence of the value of anticoagulant therapy and considers that there is no indication for such treatment as a routine, but the theoretical advantages may justify the use of anticoagulant drugs in the more seriously ill patient.

The early complications of cardiac infarction have been studied by Pearson (27) who has commented on the dangers not only from the local effects of the lesion and the circulatory depression which follows, but also from the immobility which must be imposed by the physician, together with the hazards that may attend more active treatment. The length of survival after myocardial infarction has been examined by Smith (28) who has confirmed the absence of relationship between the severity of the attack and the subsequent length of life. A longer survival time was found for women than for men in those who live into the second decade, when hypertension becomes a

more important factor in shortening the survival period. The possible mechanisms capable of augmenting or replacing the normal coronary supply following occlusive atherosclerosis have been stated by Bailey *et al.* (29) to be the development of additional vascularity at the base of the heart and in pericardial adhesions, over-development of normal intracardiac openings, and enlargement of intercoronary vascular communications.

Experimental work by Hahn *et al.* (30) suggests that satisfactory retrograde circulation through the capillary bed can be obtained by arterialisation of the coronary sinus. However, Eckstein *et al.* (31) have demonstrated that arterialisation of the coronary sinus results in a retrograde flow capable of producing only a quarter or less of the myocardial oxygen requirement. If the coronary flow is normal or reduced, myocardial anoxia results from restriction in capillary outflow. Cardio-pericardioplexy using magnesium silicate as a pericardial irritant has been performed by Thompson & Plachta (32) upon 57 patients with coronary artery thrombosis during the last 13 years, the subsequent average life duration being 5 years. Dack & Gorelik (33) basing their opinion upon three years experience with 36 patients have confirmed their opinion that this may be a useful procedure.

The prognosis of angina pectoris has been studied by Block *et al.* (34) in a large series of patients. The average age at diagnosis was 58.8 years, and the ratio of males to females was approximately 4 to 1. The mortality was greatest (15 per cent) in the first year and was approximately 9 per cent per year subsequently. Electrocardiographic abnormality was a good indication of prognosis. Obesity was found to favour survival.

Dioxyline phosphate has been found of possible value in the treatment of angina by Scott *et al.* (35). Talley *et al.* (36) considered that pentaerythritol tetranitrate was of dubious value. Binder *et al.* (37) and Port *et al.* (38) have found heparin ineffective.

VALVULAR DISEASE OF THE HEART

The prime importance of clinical signs in the differentiation of predominant mitral stenosis from predominant mitral incompetence is stressed by Logan & Turner (39) in the selection of patients for operative treatment for mitral valve disease. The quality of the first heart sound and the opening snap are diagnostic, the apical systolic murmur and atrial systolic expansion being of relatively little value. While the assessment is primarily clinical, radiography is indispensable, electrocardiography is sometimes useful in confirmation, and cardiac catheterisation is of value in difficult cases. In surveying the results of operation, it was found that a good improvement was obtained in 66 of 74 patients. Ligation of the inferior vena cava is suggested as a useful preavalvulotomy procedure in the presence of intractible edema. Wade *et al.* (40) have examined thoroughly the hemodynamic bases of the symptoms and signs in mitral valvular disease using a group of 49 patients. An inverse relation between exercise tolerance and the pulmonary arterial and capillary pressures was found, the cardiopulmonary blood volume being related directly to the pulmonary capillary pressures. Ventricularisa-

tion of the pulmonary capillary pressure curve indicated mitral incompetence and in the severer grades was associated with an apical systolic murmur although other classical signs might be absent. The degree of left auricular enlargement was greatest in the presence of auricular fibrillation, not being closely related to the height of the pulmonary capillary venous pressure. Vertical or semivertical electrical axes were almost invariably found; electrocardiographic signs of right ventricular enlargement were uncommon. Broad and bifid P waves were associated with left auricular hypertrophy. In the quantitative assessment of disability in mitral stenosis, estimation of the degree of the dominant symptom, dyspnoea, is complicated by psychological factors, and Stock & Kennedy (41) have provided a quantitative index based upon physiological change in ventilatory function during exercise. The opening snap was examined in a clinical and phonocardiographic study by Mounsey (42) who found it a useful diagnostic sign in the absence of other signs of mitral stenosis upon casual examination. It is suggested that its presence should lead to careful auscultation for the latent middiastolic murmur. Janton *et al.* (43) have analysed the results obtained by commissurotomy of a series of 100 consecutive cases of mitral stenosis. Functional improvement occurred in 78 patients, 9 were unimproved, 11 deaths were attributable to surgery, and 2 died during the three year follow-up from intercurrent infection. The methods of selection of patients for operation are reviewed in detail, and they correspond closely to the criteria concisely defined by Wood (44). Ravin *et al.* (45) have carefully examined the criteria for diagnosis of tight mitral stenosis. They note that although commissurotomy of the mitral valve has been so far limited to those suffering from this condition with a minimum of complication by other valvular involvement, it is possible to anticipate rectification of mitral stenotic pathology in patients who may suffer from other valvular lesions in view of the low mortality and good functional results. The fatalities reported by Goodwin (46) and Sancetta *et al.* (47) as a result of subendocardial trauma endorse the necessity to reserve cardiac catheterisation for those patients only where real difficulty of assessment exists.

Mitral incompetence has been studied by Brigden & Leatham (48). Its natural history is longer and more benign than that of mitral stenosis, but bacterial endocarditis is a more frequent complication. A difference in etiology or response to rheumatic disease is suggested. A complaint of palpitation attributable to multiple ventricular extra systoles is fairly common, but significant symptoms are few unless failure develops. The clinical signs consist of a loud apical murmur always filling systole and often maximal in late systole, extending up to and usually embracing the second sound with wide splitting of the second sound in some cases. The length of the systolic murmur, its position in systole, and relationship to the sounds are as important as loudness in differential diagnosis from aortic stenosis and associated mitral stenosis. Systolic expansion of the left auricle is the most important radiological sign.

The problem of the diagnosis of mitral incompetence accompanying

mitral stenosis has been reviewed by Logan (49) who emphasises the difficulty involved and doubts the value of systolic expansion of the left atrium as a sign of mitral incompetence. This problem of differentiation of the predominant lesion has met also with the attention of Venner & Holling (50). The frequent impossibility of preoperative differential diagnosis by all the means at present available is stated. Regurgitation may be small in volume in comparison with the volume of the left atrium and pulmonary veins and may be found only at operation. The esophageal piezocardiogram has been used by Lasser *et al.* (51) to record left atrial pressure curves, and proved to be a method of obtaining pressure patterns with a minimum of experimental complication. Soloff *et al.* (52) have prepared border electrokymograms of the cardiovascular silhouette to determine the importance of atrial border motion in differentiating organic from functional apical systolic murmurs. Plateau curves previously considered to be pathognomonic of organic mitral regurgitation were observed to occur also in normal subjects.

Rheumatic activity was found to be present in spite of negative clinical and laboratory findings in biopsy specimens from left auricular appendages resected at operations for mitral stenosis by Biorck *et al.* (53), indicating the necessity for long term observation to determine the importance of active rheumatic endocarditis following operation. Enticknap (54) does not consider that the lesions resembling Aschoff bodies necessarily indicate an acute rheumatic process. Gilroy *et al.* (55) have observed a striking engorgement of the pleurohililar veins during operation for mitral stenosis and at necropsy. They suggest that these veins form a decompressive mechanism in patients with pulmonary venous hypertension. A post mortem study has been made by Hall *et al.* (56) of the distribution of cerebral emboli with regard to the possibility of their prevention during operative procedures; no significant predilection for any one cerebral vessel and no disparity in distribution was found.

A survey of the results obtained by valvotomy for mitral stenosis was given in the *British Medical Journal* (57), and there was an annotation upon mitral regurgitation in the *Lancet* (58). A conservative assessment of the results obtainable by commissurotomy has been made by Werko *et al.* (59). Clinical improvement did not necessarily correlate with a return to normality of the pulmonary dynamics. It is considered that the prophylactic use of this operation is contraindicated.

CONGENITAL HEART DISEASE

In patients suffering from patent ductus arteriosus, Lewes (60) found that the mean resting pulse pressure was significantly greater than in control subjects. A fall in diastolic pressure after exercise occurred uncommonly and could not be regarded as of diagnostic significance of this lesion. McCord & Blount (61) have examined right atrial pressure curves in tricuspid regurgitation, demonstrating ventricularisation of the pressure wave. A new radiosopic sign of tricuspid atresia consisting of contraction of the posterior

cardiac border after the anterior in the left oblique position has been described by Snow (62).

Campbell & Deuchar (63) have reviewed the results of 200 anastomotic operations in patients with congenital heart disease. Excellent results followed the operative treatment of Fallot's tetralogy, 75 per cent benefited greatly against an operative mortality of 8 per cent. Less satisfactory results were obtained in the smaller number of patients who had more complex lesions; the operative indications are still to be defined.

An examination of autopsy reports upon patients with pure pulmonary stenosis has been made by Selzer & Carnes (64) who conclude that this lesion does not in itself produce cyanosis in the absence of terminal heart failure. As a component of the tetralogy of Fallot it can be regarded as compensatory, enabling the right ventricular pressure to be elevated to that of the systemic circulation, thereby permitting a right-left shunt compatible with survival. Pulmonary stenosis can be regarded as a principal factor in the production of chronic cyanosis only if there is coexisting septal patency, and its influence upon cardiac dynamics must be taken into account prior to attempts at surgical correction. A classical machinery murmur of patent ductus arteriosus may be absent in isolated cases as has been described by Bothwell *et al.* (65) if the pulmonary arterial pressure is raised to such a degree that intermittent or complete reversal of the shunt occurs.

Congenital heart disease was found to occur in 3.17 per thousand total births by McMahan *et al.* (66). A high early mortality was found, 30 to 40 per cent only surviving to 10 years of age. Associated anomalies were observed in 21 per cent of cases, there being no definite association with any single malformation. Goyette & Palmer (67) have studied post mortem 34 cases of Marfan's syndrome of arachnodactyly and cardiovascular disease. The most common lesion was cystic necrosis of the media with aneurysmal formations of the ascending aorta. Valvular lesions were uncommon and septal defects functionally insignificant although occasionally encountered.

RHEUMATIC HEART DISEASE

Experience gained during a five year period of prophylaxis of recurrences of rheumatic fever by penicillin has been described by Kohn *et al.* (68). In contrast to the use of sulphonamides, no development of resistance by Group A hemolytic streptococci was found. Penicillin is considered to be the antibiotic of choice, and it was used in oral dosage of 800,000 units per day for the first week of each month, supplemented by extra dosage during rheumatic fever seasons. Continuous prophylaxis until the age of 25 years is advocated for the rheumatic child, and the necessity for treatment of the siblings is indicated.

Hill (69) has extended the previous work upon C-reactive protein, the presence of which was a sensitive test for the degree of rheumatic activity. Changes in the concentration were found to parallel variations in the sedimentation rate (ESR), but a fall in the concentration occurred before a fall

in the latter during convalescence. The radiological diagnosis of rheumatic pericardial effusion has been studied by Besterman & Thomas (70) who found that the most consistent changes in the early stages were a sudden increase of cardiothoracic ratio and straightening of the left border. The necessity to distinguish effusions from cardiac enlargement is emphasised; cardiac catheterisation may be indicated.

A study of the gentisic acid derivatives in the treatment of rheumatic fever has been made by Clarke *et al.* (71) who claim that the gentisates are much better tolerated and are more effective than other forms of therapy. Clarke & Mosher (72) have studied the absorption and excretion of gentisic acid. Aspirin was found to be better than 3-hydroxy-phenylcinchoninic acid by Clarke & Houser (73) in the control of arthritis, fever, and raised ESR. A limited extension to the use of cortisone and ACTH has been recorded by Bach *et al.* (74) whose observations were in accord with the suggestion that salicylates exert their pharmacological activity by engendering adrenocortical excess. Golden & Hurst (75) have had the opportunity to examine the effect of treatment with cortisone upon a patient dying with acute rheumatic heart disease, finding inhibition of the inflammatory reaction without demonstrable alteration of the collagen injury.

PERICARDITIS

The distinguishing features of acute benign pericarditis of unknown etiology in differentiation from other forms are recorded by Davies (76). The onset is sudden with fever and a pericardial rub. Pleural and pericardial effusions often occur; recovery usually takes place in two or three months. Sawyer *et al.* (77) have investigated the effect upon the intracardiac pressure and blood flow in constrictive pericarditis. It is concluded that the effect upon the left ventricle is of prime importance; there is a rise in pulmonary venous pressure. The necessity for operative treatment is confirmed. The association of chronic constrictive pericarditis and rheumatic heart disease has been examined by Kaltman *et al.* (78) who conclude that the two conditions may coexist although they are not causally related. Sokoloff (79) has drawn attention to the incidence of pericarditis in patients suffering from rheumatoid arthritis.

HEART DISEASE IN PREGNANCY

A conservative assessment of the hazards of pregnancy in women with heart disease has been made by Bramwell (80). A classification into which patients may be grouped is given, and the view-point throughout is to substantiate the opinion that heart disease is no contraindication to pregnancy and that the risk in the past has been grossly exaggerated. The hazards in the main constitute congestive heart failure, pulmonary edema, and fibrillation. It is emphasized that surgical treatment is an unjustifiable risk in the management of a woman admitted desperately ill with a failing heart. Normal medical measures often convert a hopeless case into a reasonable surgical risk and relief of heart failure will often permit of normal delivery

which carries less risk than Caesarian section. Apart from a single exception of coarctation of the aorta pregnancy should be allowed to pursue its normal course, and interference is usually unjustified. Acute pulmonary edema requires special vigilance; congestive heart failure usually responds well to treatment if recognised early, and auricular fibrillation is not necessarily a bar to pregnancy provided adequate antenatal and postnatal care can be assured.

ELECTROCARDIOGRAPHY

Phillips *et al.* (81) have found that the electrocardiogram is the best single technique in cardiac case finding. All 12 leads should be recorded. However, 13 per cent of presumably normal individuals would be erroneously suspected of possible heart disease. A group of patients with pulmonary tuberculosis was examined by Fox *et al.* (82) to determine differentiation between abnormal electrocardiographs produced by cardiac displacement and those attributable to myocardial damage. P wave changes were found to be significant. RS-T changes occur sometimes in normal subjects, and their incidence is increased in pulmonary disease necessitating caution in interpretation. Comparison of accurately defined heart position at post mortem by Grant (83) with the ante mortem QRS axis deviation demonstrated that the criteria in unipolar electrocardiography for identifying the position and rotation of the heart have little validity. The left ventricle and interventricular septum have a remarkable constancy of position in normal and diseased subjects; significant rotation was not encountered. From further investigation of the mechanisms involved in auricular flutter and fibrillation, Scherf *et al.* (84) conclude that a differentiation continues to be justified. A theory is proposed by which fibrillation is characterised by the presence of multiple tachysystolic centers. A panoramic vectorcardiograph has been used by Milnor *et al.* (85) to resolve the conflicting theories upon the presentation of electrical activity by unipolar leads. Their observations suggest that these leads are not semi-direct and influenced principally by the myocardium underlying the exploring electrode but confirm the hypothesis that the unipolar leads depend more upon their axes in the cardiac electrical field than upon localised preferential conduction. The effect of prolonged cooling of the anterior chest wall upon precordial tracings has been studied by Brink & Goodwin (86) who have obtained results suggesting that repolarisation follows the same path as depolarisation, from within out and confirming that isolated T wave changes represent only superficial muscle damage. Lepeschkin & Surawicz (87) have suggested that confusion of an elevated U wave with the T wave may suggest a prolonged Q-T. The corrected Q-T duration in hypopotassemia without hypocalcemia is not prolonged. Palmer (88) has noted the rarity of reports upon isolated U wave negativity and considers empirical knowledge of its significance is overdue. Westlake *et al.* (89) have shown that crystalline digitalin (Digitoxin) changes the order of repolarisation in a predictable manner though in an unpredictable amount in both normal and abnormal hearts, by acceleration of repolarisation in subendocardial muscle with abolition of the normal ventricular

gradient. A practical spatial vector analyzer for the conventional electrocardiogram has been devised by Simmonson (90).

BALLISTOCARDIOGRAPHY

Standardization of methods of preparing records and interpreting tracings has still to be accomplished. Important contributions on standardization have been made by Rappaport *et al.* (91) in their analysis of the factors which fundamentally affect ballistocardiographs, and in the subsequent study by Thompson *et al.* (92) of the normal ballistocardiogram in which the causation of the various time relationships with allowance for phase distortion is discussed. An attempt to standardize the normal tracing has also been made by Scarborough *et al.* (93) who have noted the high incidence of abnormal ballistocardiograms in the older age groups. Using the Dock electromagnetic undamped direct ballistocardiograph, Tannenbaum *et al.* (94) have shown the HIJKL complex is related entirely to the events of ventricular systole, the M, N, and O waves occurring during diastole. The Nickerson ballistocardiogram was found by Jones (95) to show increasingly frequent abnormality of I and J waves in arteriosclerotic heart failure as opposed to other forms of heart disease in the older age groups. The alterations which take place during respiration have been examined by Gubner *et al.* (96). The status of the ballistocardiogram has been discussed by Starr (97) who has pointed out that the technique enables an assessment of the strength and the weakness of the myocardium beyond that available by any other method in current use and has suggested its use in assessing the prognosis in myocardial infarction. A consistent deformity of the early systolic portion of the complex was recorded in mitral stenosis by Davis *et al.* (98) who found it was reduced by commissurotomy.

PHONOCARDIOGRAPHY

Leatham (99) has prepared a thorough appreciation of the principles, techniques, and status of this method of investigation.

HEART FAILURE

The dynamics of heart failure have been surveyed extensively by McMichael (100, 101). In failure, the minute volume of the cardiac output is maintained initially at the expense of hypertrophy of the heart and later by congestion of the lungs with a rise in venous pressure which is at first compensatory but is later associated with a hypodynamic state of failure. In left ventricular failure, the output is sustained, therefore, at the expense of pulmonary hypertension. Digitalis is indicated in hypodynamic failure, and the uncertainty of action is occasioned by the relative effect upon the left and right heart. When failure is associated with mitral stenosis the unreliable response to digitalis is attributable to its inability to strengthen a fibrillating auricle or alter the mechanics of the sclerosed valve. but it produces a beneficial reduction in the heart rate. Commissurotomy is an especially welcome operation. The importance of differentiation of hypodynamic con-

gestion in which the administration of digitalis will be beneficial from compensatory states of congestion is emphasized.

Active pulmonary vasoconstriction has been suggested to occur in heart failure by Halmagyl *et al.* (102). Together with Kelley *et al.* (103) they have used vasodilators and have obtained a beneficial effect.

Procaine amide has been used intramuscularly by Enselberg & Lipkin (104) who have found it a safe and effective method for the treatment of cardiac arrhythmias. The value of this drug has been confirmed by Kelley *et al.* (105). Schwartz *et al.* (106) and Miller *et al.* (107) have indicated that procaine amide should not be used in atrioventricular dissociation, and Schwartz *et al.* (108) have found quinidine is also contraindicated. Miller *et al.* (109) and Hansen *et al.* (110) have used procaine amide or quinidine to restore sinus rhythm in patients with auricular fibrillation, and their results have indicated that this should be attempted.

Capps *et al.* (111) have stated that mercurial diuretics have no primary effect on the reabsorption of water, but the increased urine flow results secondarily from increased eliminations of ions. Lowe (112) has postulated a water volume controlling mechanism having restoring and disturbing components which may be partially blocked by mercurial diuretics. Moyer *et al.* (113) have reported satisfactory diuresis was obtained following oral dosage of the mercurial diuretic, Neohydrin, gastrointestinal intolerance limiting therapy in 10 per cent. The nonmercurial oral diuretic, 1-propyl-3-ethyl-6-aminouracil, was found active by Hellman *et al.* (114), but the incidence of toxic symptoms was too high to permit of clinical application.

Duncan (115) has shown that the sodium adsorption of exchange resins is of unabsorbed dietary origin rather than that contained in the intestinal secretion, and the amount varies with the degree of edema. Cation exchange resin has been found useful by Peel & Semple (116), but they emphasise the necessity for biochemical control during the early stages of treatment.

PERIPHERAL VASCULAR DISEASE

The association of angina pectoris and intermittent claudication has been reviewed by McDonald (117). Using limbs amputated following arteriosclerotic gangrene, Wessler & Schlesinger (118) have been able to compare radiographic and anatomical appearances. Their results show that radiographic findings bear no relation to the presence or location of arterial occlusions. Surprisingly rich interarterial anastomoses were found, gangrene occurs only after multiple clot formation justifying the therapeutic use of anticoagulants. Examination of the clinical circumstances preceding amputation have led Wessler & Silberg (119) to believe that fresh occlusions constitute the major danger. These are controllable by anticoagulant therapy, and antibiotics will control excessive demands upon the compromised circulation from infection. Such therapy was concluded to be of greater importance than attempts to stimulate the collateral circulation. Kinmonth & Hadfield (120) have advocated preganglionic sympathetic section in preference to ganglionectomy in the treatment of Raynaud's disease. Green *et al.* (121)

and Green & Grimsley (122) have studied antiadrenergic drugs and find Regitine active in vasospasm and arteriosclerotic disease.

HYPERTENSIVE HEART DISEASE

In view of the clinical experience of improvement in obese hypertensive patients following weight reduction, Martin (123) examined the effect upon the blood pressure. Symptomatic improvement was not accompanied by any definite fall in pressure. Droller *et al.* (124) were unable to find any significant correlation between the blood pressure and the symptoms, signs, and general condition of the patient. Excellent results have been reported by Pickering & Heptinstall (125) following excision of pyelonephritic kidneys, but malignant hypertension was not improved. Unilateral renal disease may cause severe and accelerated hypertension; the importance of early recognition has been emphasised since there is a prospect of cure by nephrectomy. The blood pressure was restored to normal by nephrectomy in 20 of a series of 40 patients studied by Perera & Haelig (126).

The pathogenesis of malignant hypertension has been reviewed by Pickering (127). It is suggested that the arteriolar lesions depend only upon the level of the pressure in the artery, and that papilledema is the direct result of a severe increase in diastolic pressure. Malignant hypertension is regarded as a syndrome of albuminuric retinitis, rapidly progressive renal failure, and postmortem evidence of arteriolar necrosis. This syndrome may follow in all the conditions associated with severe hypertension should the diastolic pressure rises to high levels, usually over 140 mm. Hg, but subject to individual variations. Regression is possible if the pressure can be lowered in time. The symptomatology and clinical signs presenting in a group of 104 cases of malignant hypertension have been examined by Schottstaedt & Sokolow (128) who have found an average age of onset of 42 years. They consider that an increase in survival time is to be expected if vigorous therapy is applied before renal function is impaired and there is irreversible damage to cerebral vessels and the heart. A useful standard of course and prognosis of hypertension in the absence of specific hypotensive measures has been supplied by Leishman (129). Obesity and hypertension proved a favourable combination. He regards malignant hypertension as an accelerated form of the disease, and a benign slowly progressive hypertension is recognized as the most common form and has a good prognosis. The rapidity of development of vascular changes appear to be governed by the height of the diastolic pressure, the critical level suggested being 130 mm. Hg.

Allen (130), Morissey *et al.* (131), and D'Abreu (132) have stated that sympathectomy is of value in the treatment of hypertension, but it is acknowledged that this operation should be resorted to only in the absence of a response to medical treatment. Adrenalectomy has been advocated by Thorn *et al.* (133) and Green *et al.* (134), and subtotal adrenalectomy has been combined with sympathectomy by Wolferth *et al.* (135). The value of adrenalectomy has been disputed by Merrill (136).

Further experience with a number of drugs active in reducing the blood

pressure has been recorded. Moyer & Caplovitz (137) have confirmed the hypotensive action of Regitine but found its therapeutic use was limited by development of tolerance and by intestinal irritation precluding oral dosage. Scott *et al.* (138) found that oral administration of a mixture of dehydrogenated alkaloids of ergot (C.C.K. 179) produced a marked fall in blood pressure and improvement in hypertensive patients. The activity of protoveratrine and its suitability for clinical use have been defined by Meilman & Krayer (139). A thiophanium derivative (Ro 2-2222) has been examined by Sarnoff *et al.* (140) particularly in regard to its use in the management of acute pulmonary edema. Redisch *et al.* (141) have used a Dibenamide analogue. A further clinical examination of the effect of hexamethonium has been made by Morrison (142) who has confirmed the hypotensive activity and usefulness of this drug in the treatment of hypertension. Morrison & Paton (143) have advanced the information available upon its effect on the normal subject. New homologues of hexamethonium have been described by Maxwell & Campbell (144) which are considered to be of potential greater usefulness in the management of hypertension than the original drug. The control of hypertension has been reviewed by Platt (145) who has endorsed the value of hypotensive drugs.

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