8

Some Observations on the Effect of Certain Drugs on the Human Blood Pressure

Thesis for the Degree of M.D. 1 Jan 1914

by

Allan Watson, M.B., Ch.B.

Lieutenant, Royal Army Medical Corps.

Some Observations on the Effect of Certain Drugs on the Human Blood Pressure.

The investigations hereafter recorded were made with the object of determining what effect, if any, certain drugs, commonly supposed to act as blood pressure elevators, have on the systolic and diastolic pressure of healthy individuals.

My observations have been limited to the immediate effect of the drugs experimented with, as one of the objects of the research was to endeavour to compare their values as possible remedies for combating dangerous hypotension.

Most of the statements made regarding the pressor action of certain medicaments are based on the results of laboratory experiments on animals, and the conclusions so formed, as has been frequently demonstrated, do not always hold when drugs are given to patients in ordinary doses.

My observations have been made on persons with normal arterial tension rather than on patients suffering from marked hypotension; partly because of the difficulty or impossibility in such cases of insuring with reasonable certainty that the blood pressure of the patient remains unaffected by anything but the drug administered, but chiefly because the condition of the vessels in cases of marked hypotension has not yet been definitely determined. Until recently Crile's/

Crile's theory (Surgical Shock, 1899), that the vessels are relaxed in those cases as a result of exhaustion of the vaso-motor centre, has been generally accepted; but the opposite view first put forward by Malcolm (The Physiology of Death from Traumatic Fever, 1893), that there is a general contraction of the vessels, has now many supporters.

Most of my observations were made on the effect of drugs on my own blood pressure. I am 26 years of age, in sound health, and have an average systolic and diastolic pressure of about the generally accepted normal. In a few instances the conclusions arrived at were confirmed by observations made on other healthy individuals. In order that the results obtained might be comparable, every care was taken during the investigations to maintain as nearly identical conditions as practicable, and to exclude as well as possible all transitory factors influencing the normal arterial tension.

There is not, as far as I am aware, any published record of a similar series of investigations, but Edgecombe (Practitioner, April 1911, pp. 531-536) has recorded his observations on the sustained effect of certain reputedly pressor drugs when administered for several days to a subject with a persistently low blood pressure.

Method Employed to Take Blood Pressure Readings.

The blood pressure readings in all my investigations were taken with the same instrument. The one I employ is French's modification of the Riva-Rocci sphygmomanometer. It is fitted with a Verdon armlet, which measures undistended 14 cm. in width. French's sphygmomanometer, as sent out by the makers, is not graduated below 40 mm.Hg., but as I met with lower pressures I had additional graduations made on the instrument below this mark.

All readings were taken in the sitting posture, the armlet being applied to the left upper arm at the heart level. Care was taken to keep the arm perfectly flaccid during the observations, and to have the breathing as quiet as possible.

Korotkow's auscultatory method was invariably employed to determine the systolic and diastolic blood pressure. The procedure I followed was to first rapidly raise the pressure in the apparatus, with the armlet adjusted in position, until the lumen of the brachial artery was obliterated. The pressure was then slowly decreased and the systolic blood pressure was read at the point at which the first pulsation bruit was heard through an ordinary binaural stethoscope, the bell of which was placed over the brachial artery immediately below the lower edge of the armlet. The pressure was still further decreased and the height

of/

of the mercury column at the instant at which the bruit disappeared entirely was taken to indicate the diastolic blood pressure.

That the maximum or so-called systolic pressure as determined in this manner is accurate has been recently proved by records made on the Erlanger instrument by Warfield (Interstate Medical Journal, Vol. XIX, p.860) Authorities differ as to the value of the methods at present available for estimating clinically the minimum or so-called diastolic pressure, but according to Faught (Blood Pressure, 1913 p.50), and other recent writers the auscultatory method as above described gives the most reliable readings.

Preliminary Observations.

Before investigating the effect of any drugs on myself, numerous observations were made on my blood pressure for several weeks in order to determine in what circumstances it could be kept at the most approximately uniform level. The average systolic and diastolic pressure was determined, the effect of various factors known to influence the blood pressure was noted, and lastly series of frequent observations were made to discover how uniform the readings would remain when the influence of those factors was as well as possible excluded. I do not propose to give details of those observations, as they do not properly form a part of the thesis.

The average systolic pressure was found to be about 125 mm. Hg; the highest systolic pressure observed was 146 mm. Hg, and the lowest 110 mm. Hg. The average diastolic pressure was about 64 mm. Hg; the highest diastolic pressure observed was 76 mm. Hg, and the lowest 42 mm. Hg. There was very little difference between the average forenoon, afternoon and evening readings.

The effect of digestion, stimulants, smoking, mental work, and physical work were each investigated on several occasions, but in no case did these factors produce effects which differed particularly from those found by other observers. On every occasion, any

effect/

effect produced had passed off in less than an hour and a half.

Nine series of frequent observations on my blood pressure and pulse rate were then made, each series extending over a period of about three hours. For two hours before they commenced, and while they were in progress, I endeavoured to do nothing which would be likely to affect the blood pressure or pulse rate; and for about half an hour before they commenced, and while they were in progress I remained seated in one room the temperature of which remained approximately uniform.

When a series of frequent observations were being made care was taken to have the sphygmomanometer armlet quite relaxed between the readings, as they would of course have been affected by any continuous pressure. It was found that the systolic and diastolic pressures varied very little if, at the commencement of a series of observations, they corresponded fairly closely to the average pressures already noted. On the other hand if they were abnormally high or low at the commencement of a series of observations they generally fell or rose to about normal in the course of half an hour or so. The systolic pressure was found to be decidedly the more stable of the two, comparatively slight physical or mental stimuli causing the diastolic pressure to fall or rise considerably for a few minutes. The pulse rate on every occasion varied scarcely at all.

Method Employed to Investigate Action of Drugs.

Most of the drugs used in those experiments are commonly employed in practice and all had been obtained from firms of chemists of repute. One or more series of observations were made on the effect of the generally accepted maximum dose of each drug; observations on the effect of smaller and larger doses were also made in most cases. The drugs were administered hypodermically, the injections being made into the right forearm. At least two days were allowed to elapse between each experiment in order to be certain that the effect of the last dose had passed off completely before administering another.

Before a series of observations commenced, and while they were in progress, similar precautions were taken to those mentioned as having been taken during the preliminary observations, to exclude as well as possible anything but the drug administered from affecting the blood pressure or pulse rate. In order that the results obtained might be comparable, all the investigations were made in as nearly identical conditions as practicable. Before a drug was administered blood pressure readings were taken at intervals of from 10 - 25 minutes for an hour or so, with the object of supplying a basis for comparison, and of determining if they corresponded reasonably closely to the average readings previously ascertained. When discrepancies were at all marked, as occasionally happened, the experiment/

experiment was abandoned for the time being; otherwise the drug to be investigated was then administered, and frequent observations on the blood pressure and pulse rate were commenced forthwith. When any effect on the blood pressure was produced the observations were continued until this effect had passed off. When no appreciable effect was produced the observations were continued for at least an hour. No series of observations have been recorded in which the blood pressure was obviously affected by some accidental occurrence while they were in progress.

In the accounts of the experiments which follow, the times given indicate to within half a minute the time at which the reading of the systolic pressure was taken, the diastolic pressure was read a second or two later, but about a minute or so was allowed to elapse before the pulse rate was noted, in order to avoid to some extent any slight accelerator effect which the taking of the blood pressure might have had on it.

Adrenalin.

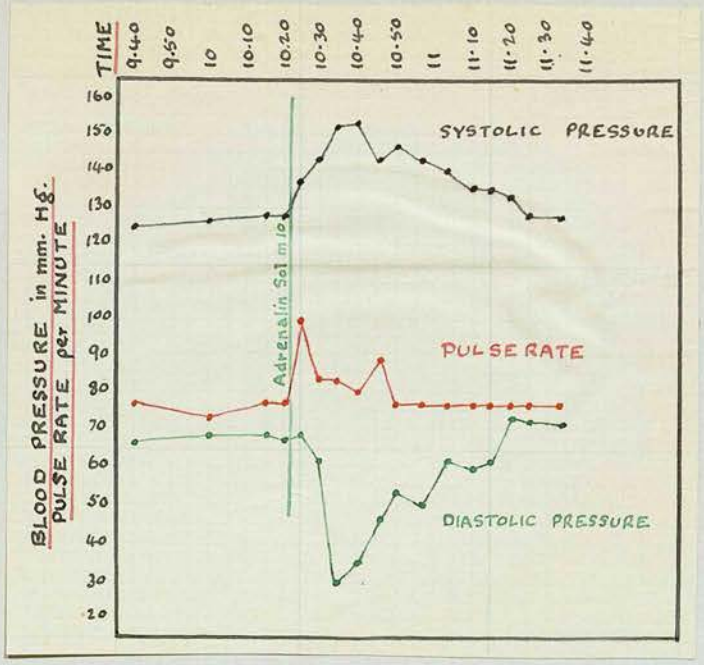
Extract of the suprarenal gland was first shown to constrict the bloodvessels by Schäfer and Oliver (Journal of Physiology 1895, Vol.XVIII, p.230). More recently Cow, (Proceedings of Royal Society of Medicine, 1911, Vol.IV, Part III, Pharmacological Section, pp.81-82) and other observers have noted that the effect of this drug on different bloodvessels varies considerably; some are powerfully constricted, some slightly constricted, and some are dilated.

The general opinion appears to be that adrenalin is an effective remedy for hypotension, when administered intravenously with a quantity of saline solution, but this method of administration was scarcely practicable in the case of healthy subjects. Reports are conflicting as to its value as a blood pressure elevator when given hypodermically. Hale-White, (Materia Medica, 1911, p.635), Faught, (Blood Pressure, 1913, p.266) and Scott (Practitioner, August, 1912, p.259) are of the opinion that when so administered its characteristic pressor effect is produced. On the other hand Cushny, (Pharmacology and Therapeutics, 1910, p.337) Dixon, (Practitioner, March, 1911, p.362) and Lemann (American Journal of Med. Science, 1911, II, p.865) consider that when hypodermically administered in ordinary doses adrenalin generally has no effect on the blood pressure.

I/

I made four separate series of observations on the effect of adrenalin when administered hypodermically. The preparation used was the 1 in 1000 solution of adrenalin chloride in normal saline solution made by Parke, Davis, & Co. Two series of observations were made on the effect of 10 m of this solution on my blood pressure, and the effect of the same dose was also observed on two other healthy subjects. The drug in every case caused a marked elevation of the systolic pressure and an even more marked depression of the diastolic pressure. This action of adrenalin on the diastolic pressure has not, I believe, been previously recorded.

The first series of observations were made on the effect of 10 m of the 1 in 1000 solution on myself. The effect on the blood pressure and pulse rate is shown by the following chart:-



The systolic pressure was considerably elevated two minutes after the drug was administered; it remained elevated for 55-60 minutes. The maximum height (153 mm. Hg.) was attained in about 17 minutes, and was 25.5 mm. Hg. higher than the average systolic pressure observed before the experiment commenced. The diastolic pressure began to fall 7-12 minutes after the drug was administered, and remained low for 40-45 minutes. The lowest point observed (30 mm. Hg.) was reached in 12 minutes, and was 37.75 mm. Hg. lower than the average diastolic pressure observed before the experiment commenced. The pulse rate was considerably accelerated two minutes after the drug was administered, and remained rather rapid for about 25 minutes.

A sensation of faintness and tremulousness was noted about three minutes after the drug was administered. A minute or two later the breathing was observed to be/

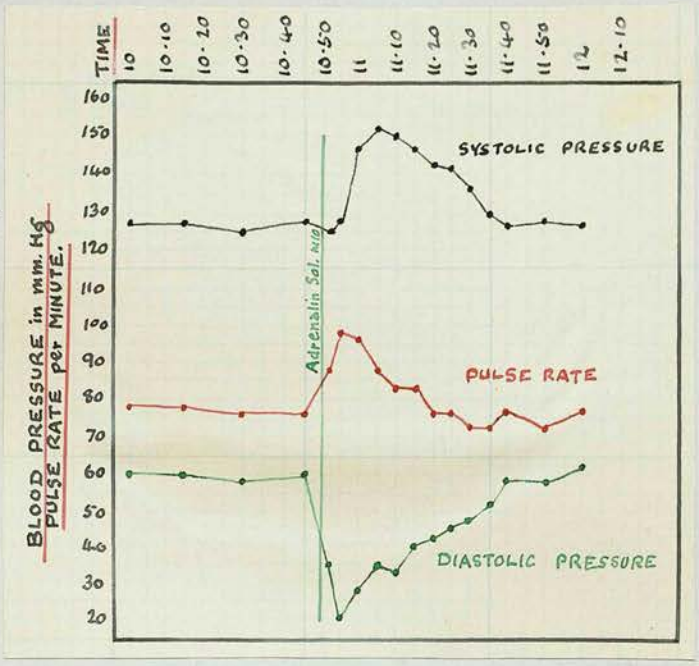
be unusually deep. The faintness passed off in about 10 minutes, but the tremulousness persisted for over half an hour, and the deep breathing for about 40 minutes.

The observations made in this experiment are shown in the following table:-

Adrenalin Table I.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse rate per Minute	
9.40	125	66	59	76	
10	127	69	58	74	
10.15	129	69	60	76	
10.20	129	67	62	76	
10.23	Adrenalin Chloride sol. m.10.				
10.25	136	68	68	100	Faint & tremulous Breathing deep.
10.30	143	62	81	84	
10.35	152	30	122	84	
10.40	153	35	118	80	Faintness gone.
10.46	143	46	97	88	
10.50	146	54	92	76	
10.57	143	50	93	76	
11.3	140	62	78	76	Tremor gone.
11.10	135	60	75	76	Breathing normal.
11.15	135	62	73	76	
11.20	134	74	60	76	
11.25	128	73	55	76	
11.33	128	71	57	76	

The effect of the adrenalin on the blood pressure and pulse rate in the second experiment on myself is shown by the following chart:-



The systolic pressure in this case did not begin to rise until 5-10 minutes after the drug was administered. The maximum height (152 mm. Hg.) was attained in about 15 minutes, and was 24.75 mm. Hg. higher than the average systolic pressure observed before the experiment commenced. The elevation of the systolic pressure persisted for 30-35 minutes. The diastolic pressure had fallen considerably two minutes after the drug was administered, and remained low for about 45 minutes. The lowest point observed (20 mm. Hg.) was reached/

reached in 5 minutes, and was 39.5 mm. Hg. lower than the average diastolic pressure observed before the experiment commenced. The pulse was increased in rate two minutes after the drug was administered, and it remained accelerated for about 23 minutes.

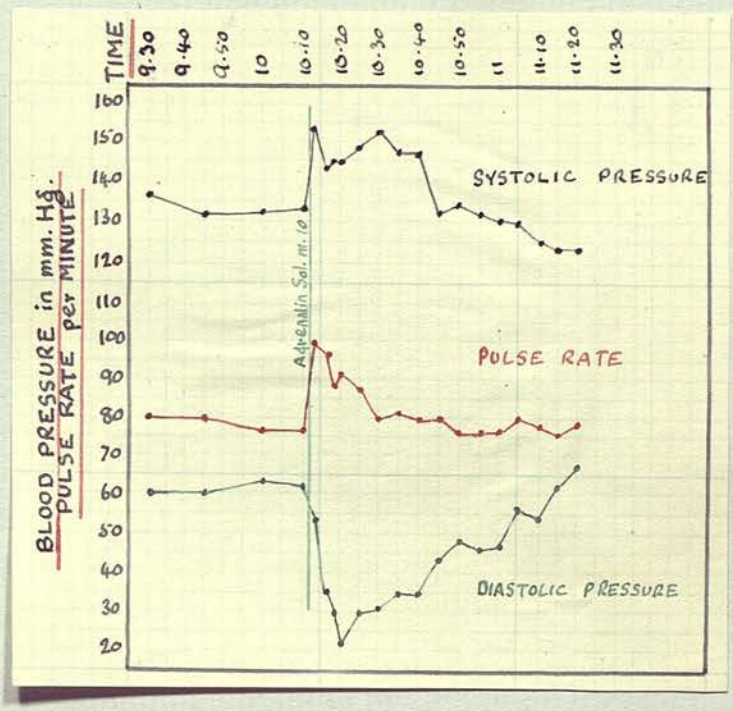
The same sensations were experienced in this experiment as in the last, but they were not so marked.

Details of the observations made are shown in the following table:-

Adrenalin. Table II.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.	
10	128	60	68	78	
10.15	128	60	68	78	
10.30	125	58	67	76	
10.45	128	60	68	76	
10.50	Adrenalin Chloride sol. m.10.				
10.52	125	35	90	88	
10.55	128	20	108	98	Slightly faint & tremulous.
11	146	28	118	96	Breathing deep.
11.5	152	35	117	88	Faintness gone.
11.10	150	34	116	84	Tremor gone.
11.15	146	40	106	84	
11.20	143	42	101	76	
11.25	142	45	97	76	
11.30	136	47	89	74	Breathing normal.
11.35	130	52	78	74	
11.40	126	58	68	76	
11.50	128	58	70	74	
12	126	62	64	76	

One series of observations on the effect of 10 m. adrenalin solution were made on D. M., a healthy male subject, age. 24 years. The following chart shows the effect of the drug on his blood pressure:-



This subject's systolic pressure shot up from 134 mm. Hg. to 154 mm. Hg. one minute after the drug was administered, but as it had fallen considerably two minutes later I think this initial rise was probably the result of nervousness. Leaving the initial rise out of account the greatest systolic pressure observed (153 mm. Hg.) occurred 17 minutes after the drug was administered, and was 29.25 mm. Hg. higher than his average systolic pressure observed before the experiment commenced. His systolic pressure remained elevated for/

for 25-30 minutes. His diastolic pressure had fallen one minute after the drug was administered, and remained low for 55-60 minutes. The lowest point observed (22 mm. Hg.) was reached seven minutes after the experiment commenced, and was 39.75 mm. Hg. lower than the average diastolic pressure observed before the drug was administered. His pulse became more rapid one minute after the drug was administered and remained accelerated for about eleven minutes.

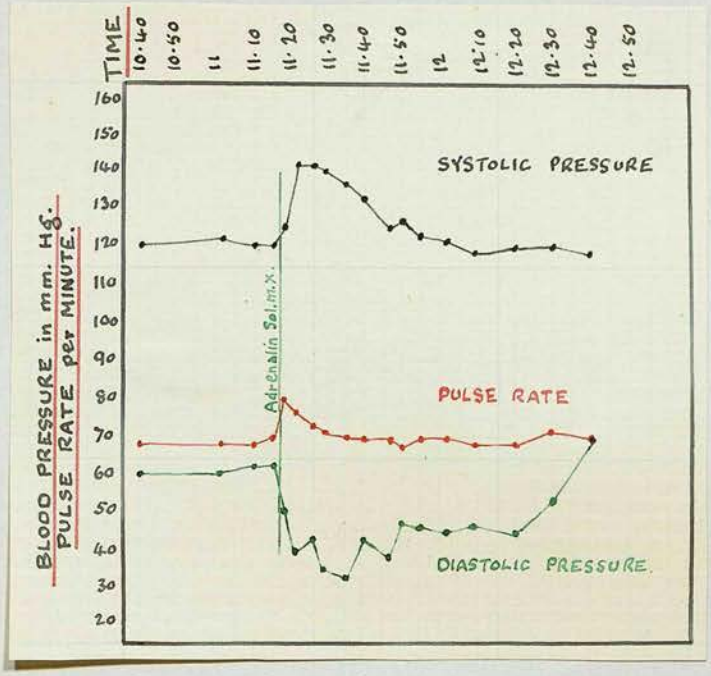
This subject also noted that he became faint and tremulous, and was breathing unusually deeply a minute or two after the drug was administered. He complained of palpitation about two minutes later.

The observations made in this experiment are shown in the following table:-

Adrenalin. Table III.

Time	Systolic Pressure.	Diastolic Pressure.	Pulse Pressure.	Pulse Rate per Minute.	
9.30	136	60	81	80	
9.45	132	60	72	80	
10	133	64	69	76	
10.10	134	63	71	76	
10.13	Adrenalin chloride sol. m.10.				
10.14	154	54	100	100	Faint tremulous & breathing deep.
10.16	143	35	108	96	Palpitation.
10.18	144	30	114	88	
10.20	144	22	122	92	
10.25	148	30	118	88	Faintness and tremor gone.
10.30	153	32	121	80	
10.35	146	35	111	82	
10.40	146	35	111	80	Palpitation gone.
10.45	134	44	90	80	
10.50	135	48	87	76	Breathing normal.
10.55	133	46	87	76	
11	131	47	84	76	
11.5	130	56	74	80	
11.10	125	55	70	78	
11.15	124	63	61	76	
11.20	124	68	56	78	

The last series of observations on adrenalin were made on W.N.W., a healthy male subject, age 24 years. The effect of the drug on his blood pressure and pulse rate is shown by the following chart:-



The systolic pressure was elevated five minutes after the drug was administered and remained high for 30-35 minutes. The maximum elevation (142 mm. Hg.) was attained in five minutes, and was 22.5 mm. Hg. higher than the average systolic pressure observed before the experiment commenced. The diastolic pressure had fallen two minutes after the drug was administered and remained low for 70-80 minutes. The lowest point observed (33 mm. Hg.) was reached in 18 minutes, and was 28 mm. Hg. lower than his average diastolic pressure observed before the experiment commenced. The pulse rate/

rate was accelerated two minutes after the drug was administered and remained rather rapid for about 12 minutes.

This subject noted the same sensations that had been observed in the other experiments. He particularly remarked on the way the drug affected his respiration.

The observations made in this experiment are shown in the following table:-

Adrenalin. Table IV.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate Per Minute.	
10.40	120	60	60	68	
11.2	122	60	62	68	
11.10	120	62	58	68	
11.15	120	62	58	70	
11.17	Adrenalin Chloride sol. m.10.				
11.19	125	50	75	80	Palpitation and tremor.
11.22	142	40	102	76	Slightly faint.
11.25	141	44	97	74	Breathing very deep.
11.29	140	35	105	72	
11.35	137	33	104	70	Palpitation & tremor gone.
11.40	134	43	91	70	Faintness gone.
11.46	125	38	87	70	Breathing normal.
11.50	126	47	79	68	
11.55	123	46	77	70	
12.2	121	45	76	70	
12.9	119	46	73	68	
12.20	120	45	75	68	
12.30	120	54	66	72	
12.40	119	70	49	70	

The effect of the adrenalin in all those experiments was to decrease the diastolic pressure more than it raised the systolic; also in three out of the four experiments the persistence of the diastolic fall was greater than the persistence of the systolic elevation.

It is generally stated that the diastolic pressure denotes the freedom or otherwise of the peripheral outflow from a vessel. Adrenalin can be so clearly proved to cause contraction of the peripheral vessels that the great depression of the diastolic pressure which it produces cannot be due to a diminished peripheral resistance, and hence it would seem that it must be accounted for by there being some freedom of outflow at the aortic orifice for the blood in the arteries.

The condition of the systolic and diastolic pressure produced by the adrenalin in my experiments resembles that shown by Gordon (Edinburgh Med. Journal, Jan., 1910, p.34) to be commonly found in cases of aortic regurgitation, and suggested to me that one of the physiological actions of adrenalin in man might be to dilate the aortic orifice and produce a temporary regurgitation. According to Gibson (Edinburgh Med. Journal, March 1911, pp. 201-211) temporary aortic regurgitation may occur in cases with high arterial pressure, owing to stretching not only of the fibrous and elastic tissue forming the aorta, but also of the muscular fibres surrounding the aortic orifice. Since a temporary high pressure may produce a stretching of/

of the aortic orifice, it does not seem improbable that adrenalin may also do so. But this condition, if it occurs, must be due to the direct action of the drug, and not to the high systolic pressure it produces, as the systolic elevations observed in my experiments were no higher than those which may be produced in healthy individuals by a variety of normal conditions, and further, the depression of the diastolic pressure in two of my experiments occurred before the systolic elevation. I am not aware if anyone has investigated the action of adrenalin on the aortic orifice, but as Cow (loc. cit.) has shown that it dilates the coronary arteries, it is not difficult to imagine that it may also dilate this part of the aorta.

During two of the investigations which have been recorded, and on another occasion when 10 m. of the 1 in 1000 solution of adrenalin was administered to one of the subjects, the aortic area was auscultated at frequent intervals. The normal aortic second sound of the subjects examined (D.M. and myself) is clear and well defined, but when under the influence of the drug it was faint and soft, although no definite murmur was detected. I am indebted to Dr T.S. Logan for having kindly confirmed the altered character of the sound in my own case.

I venture to suggest that these observations on the effect of hypodermic injections of adrenalin explain the cause of the sudden collapse or death which has occasionally followed the injection of the drug into/

into patients anaesthetised with chloroform. Such cases have recently been recorded by Depree (British Med. Journal, Vol. I, 1913, p. 879) and by Blumfeld and others (Proceedings of Royal Society of Medicine, 1911, Vol.IV., No.5, pp. 28-30). Those disasters have generally occurred in an early stage of anaesthesia when the patients were but lightly under, and, as is well recognised, this stage is the one in which death from sudden heart failure is most liable to occur. Aortic regurgitation would of course always contra-indicate the use of chloroform were the condition discovered before an anaesthetic was commenced.

A short account of those observations on adrenalin has already been published (Practitioner, Vol.I., 1914, pp.94-99.)

Atropine.

It is usually stated that atropine primarily stimulates the medullary vaso-motor centre and that consequently the blood pressure rises considerably, though it subsequently falls. At least one recent writer recommends the use of this drug as a blood pressure elevator (Williams, Clinical Journal, May 18th, 1910, p.93).

Three series of observations were made on the effect of atropine sulphate on my blood pressure. One series was made on the effect of $\frac{1}{100}$ grain, and two series on the effect of $\frac{1}{50}$ grain. Observations were made on each occasion for over an hour after the drug had been administered, but in no case was the systolic or diastolic pressure appreciably affected. The pulse rate appeared to be somewhat slowed by $\frac{1}{100}$ grain of atropine sulphate and accelerated by $\frac{1}{50}$ grain. Some dryness of the mouth was noticed on each occasion.

The observations made are shown in the following tables:-

Atropine. Table I.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
3.15	131	58	73	72
3.30	127	60	67	68
3.35	130	62	68	68
4.10	129	63	66	70
4.14	Atropine Sulphate gr $\frac{1}{100}$			
4.16	132	60	72	68
4.20	132	62	70	68
4.25	128	59	69	68
4.30	127	56	71	54
4.35	131	60	71	52
4.40	130	62	68	56
4.45	129	61	68	60
4.50	129	60	69	64
4.55	128	60	68	62
5	130	56	74	60
5.5	130	62	68	60
5.10	129	62	67	60
5.15	128	63	65	60
5.20	128	58	70	60
5.25	130	60	70	58
5.30	129	64	65	58

Atropine. Table II.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
8.10	124	56	68	64
8.25	126	54	72	68
8.45	126	53	73	66
9.5	122	57	65	60
9.12	Atropine Sulphate gr $\frac{1}{50}$			
9.15	126	57	69	60
9.20	125	55	70	60
9.25	125	53	72	58
9.30	123	57	66	60
9.35	122	58	64	64
9.40	123	56	67	60
9.45	123	54	69	76
9.50	120	58	62	76
9.55	120	58	62	80
10	122	56	66	80
10.5	123	54	69	78
10.10	123	56	67	80
10.15	124	56	68	78
10.20	126	55	71	72
10.25	122	52	70	72
10.30	123	53	70	70

Atropine. Table III.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure	Pulse Rate per Minute
5.30	129	58	71	68
5.45	128	60	68	72
6	130	63	67	72
6.20	129	60	69	72
6.23		Atropine	gr. $\frac{1}{50}$	
6.25	130	58	72	72
6.30	129	58	71	80
6.35	130	58	72	72
6.40	132	60	72	76
6.45	130	61	69	76
6.50	129	60	69	80
6.55	129	60	69	84
7	128	57	71	84
7.5	130	58	72	84
7.10	128	58	70	80
7.15	128	60	68	84
7.20	128	58	70	82
7.25	131	56	75	78
7.30	130	57	73	74

Camphor.

Camphor is classified by Cushny (Pharmacology and Therapeutics, 1910, p.725) as a drug which contracts the vessels and raises the blood pressure. Hirschfelder (Diseases of Heart and Aorta, 1913, p.252) states that it is a stimulant to the vaso-motor centre, but that its effects vary in different individuals. It is, I believe, largely used on the continent as a cardio-vascular stimulant, but its value for this purpose has recently been doubted. According to McKenzie (Diseases of the Heart, 1913, p.354) it is absolutely without detectable effect on the heart and blood vessels when administered to the human subject in medicinal doses.

The effect of the drug on my blood pressure was investigated on four occasions. The preparation used was the sterilised solution in olive oil made by Burroughs, Wellcome and Co. The effect of .1 gram (1.5 grains) was investigated on one occasion, the effect of .2 gram (3 grains) on two occasions, and the effect of .3 gram (4.5 grains) on one occasion. In no case was the camphor observed to have any effect on the blood pressure or pulse rate.

The observations made are shown in the following tables:-

Camphor. Table I.

Observations made on self before and after administration of 0.1 grm. (1.5 grs.) camphor.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
9.45	127	67	60	76
10	129	65	64	74
10.20	129	66	63	72
10.30	128	67	61	72
10.32		Camphor 0.1 grm.		
10.34	129	66	63	72
10.38	128	68	60	72
10.44	127	66	61	72
10.55	128	66	62	70
11.7	125	66	59	70
11.15	126	69	57	72
11.25	127	66	61	70
11.35	126	64	62	72
11.45	127	65	62	72

Camphor. Table II.

Observations made on self before and after administration of 0.2 grm. (3 grs.) camphor.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
5.30	123	67	56	78
5.45	120	66	54	80
6.10	121	68	53	78
6.25	122	69	53	78
6.30	Camphor 0.2 grm.			
6.32	121	68	53	80
6.35	124	66	58	80
6.40	121	66	55	80
6.45	122	66	56	80
6.50	122	68	54	80
6.55	122	68	54	80
7	121	69	52	78
7.5	124	70	54	78
7.10	121	63	58	80
7.14	121	66	55	80
7.20	118	68	50	78
7.25	119	66	53	76
7.35	121	66	55	80

Camphor. Table III.

Second series of observations on self before and after administration of 0.2 grm. (3 grs.) camphor.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
9.25	125	58	67	70
9.45	127	58	69	70
10.5	126	59	67	72
10.30	125	58	67	70
10.35	Camphor 0.2 grm.			
10.37	125	58	67	70
10.40	124	56	68	70
10.45	126	58	68	70
10.50	125	60	65	68
10.55	125	61	64	70
10.58	124	60	64	70
11.5	126	61	65	72
11.10	125	58	67	72
11.15	123	60	63	70
11.20	125	60	65	72
11.25	126	61	65	70
11.35	126	57	69	70
11.45	124	57	67	68

Camphor. Table IV.

Observations made on self before and after administration of 0.3 grm. (4.5 grs.) camphor.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
8.30	129	66	63	70
8.45	126	66	60	70
9.5	130	64	66	70
9.20	128	64	64	72
9.27	Camphor 0.3 grm.			
9.30	129	66	63	70
9.35	130	65	65	68
9.40	130	65	65	70
9.45	127	65	62	70
9.50	128	68	60	68
9.55	127	68	59	68
10	130	66	64	68
10.5	128	64	64	68
10.10	128	65	63	68
10.15	128	68	60	70
10.20	126	66	60	72
10.25	128	65	63	68
10.30	130	68	62	68

Cotarnine.

Cotarnine is said to be a vaso-constrictor and is supposed to act directly on unstriped muscle (Fortescue-Brickdale, Guide to the Newer Remedies, 1910, p.135). Marfori (quoted by Whitla, Materia Medica, 1910, p.605) maintains however that it has no vaso-constrictor action.

Three series of observations were made on the effect of cotarnine hydrochloride on my blood pressure. Two series were made on the effect of $\frac{1}{2}$ grain and one series on the effect of 1 grain. In no case was any appreciable effect on the blood pressure or pulse rate observed, nor were any unusual sensations experienced.

The observations made are shown in the following tables:-

Cotarnine. Table I.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
8.30	131	58	73	68
8.50	128	56	72	70
9.10	130	56	74	72
9.20	129	57	72	72
9.23	Cotarnine gr.½			
9.26	131	55	76	68
9.30	130	51	79	68
9.35	129	58	71	68
9.40	129	53	76	70
9.45	130	56	74	68
9.50	131	55	76	70
9.55	130	56	74	72
10	129	56	73	68
10.5	129	58	71	68
10.10	128	55	73	68
10.20	130	55	75	68
10.30	130	57	73	72

Cotarnine. Table II.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
5.45	126	66	60	80
5.10	130	60	70	70
6.25	128	62	66	68
6.35	128	63	65	68
6.38		Cotarnine	gr. $\frac{1}{2}$	
6.40	128	65	63	68
6.43	129	63	66	70
6.46	130	66	64	68
6.50	129	64	65	68
6.55	130	67	63	68
7	128	64	64	68
7.5	130	64	66	68
7.10	130	64	66	70
7.15	130	66	64	70
7.20	128	65	63	72
7.25	128	63	65	70
7.30	131	64	67	68
7.40	129	62	67	70

Cotarnine. Table III.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure	Pulse Rate per Minute.
5.30	126	66	60	68
5.50	126	62	64	68
6.10	123	64	59	70
6.25	125	63	62	68
6.32	Cotarnine gr. 1			
6.35	126	65	61	70
6.40	128	65	63	70
6.45	128	68	60	68
6.50	126	66	60	68
6.55	123	63	60	68
7	123	63	60	68
7.5	124	65	59	68
7.10	127	63	64	70
7.15	125	66	59	68
7.20	122	68	54	66
7.25	124	66	58	66
7.30	124	62	62	68
7.35	127	64	63	68
7.40	125	65	60	66

Digitoxin.

Most of the writers on the subject in textbooks and medical journals maintain that one of the important actions of digitalis is to raise the blood pressure. This action is generally stated to be due partly to the constriction of the vessels it produces by direct action on their muscular coats, and partly to the fact that it augments the strength of the cardiac contraction. Those statements are based chiefly on the results of animal experiments, but Briggs and Cook (Johns Hopkins Hospital Reports, 1903, vol.XI, p.515), experimenting on patients suffering from surgical shock, say that digitalin has a rapid but transitory pressor effect.

On the other hand, Cow (Proceedings of the Royal Society of Medicine, 1911, vol.IV, Pt.III, Pharmacological Section, p. 84) found that the effect of digitalis when applied directly to arteries was only slight; some were constricted, and others, such as the gastric and hepatic, were first slightly constricted and then dilated. Thorn (Practitioner, April, 1912, pp.593-598) claims to have proved that the comparative strength of the cardiac systole has no material effect on the blood pressure. McKenzie (Diseases of the Heart, 1913, p.377) states that digitalis raises the blood pressure in the human subject only in rare instances, and lowers it in a great number. Price

(British/

(British Medical Journal, 1912, vol.II, p.691) records a number of observations on the effect of repeated doses of the drug on the systolic pressure of several patients; he found that the pressure was not increased in any case, and was lowered in a few.

Two series of observations were made on the effect of $\frac{1}{50}$ grain of digitalin (amorphous) on my blood pressure and pulse rate, one series was made on the effect of $\frac{1}{250}$ grain of digitalin (crystalline). Both those preparations were obtained from Burroughs, Wellcome, & Co. Digitalin (amorphous) is said to consist of a glucoside resembling digitoxin, or of a mixture of digitalin and digitoxin; digitalin (crystalline) is said to consist almost entirely of digitoxin. Two series of observations were made on the effect of 15 mins. of digalen, a sterile standardised solution of amorphous digitoxin (Cloetta) obtained from the Hoffmann - La Roche Chemical Co.

Digitoxin is said to be much the most active prinicple of digitalis, and it is also said to act more powerfully on the vessels than some of the others; in none of my experiments however was the blood pressure or pulse rate appreciably affected. A rather severe local reaction about the site of injection occurred in every case; this was least marked after the injection of digalen.

The observations made in those experiments are shown in the following tables:-

Digitoxin. Table I.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
7.30	128	58	70	78
7.50	125	58	67	74
7.10	126	55	71	76
7.30	128	57	71	78
8.37	Digitalin (amorphous) gr. $\frac{1}{50}$			
8.40	125	50	75	78
8.45	125	55	70	78
8.50	125	57	68	74
8.55	128	56	72	74
9	126	56	70	78
9.10	125	56	69	78
9.20	128	55	73	76
9.30	128	57	71	76
9.40	127	58	69	76
9.50	126	55	71	76
10	128	57	71	74
10.10	125	55	70	74
10.20	128	58	70	76
10.30	125	60	65	78
10.40	128	57	71	76

Digitoxin. Table II.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
6	129	58	71	72
6.25	127	56	71	72
6.45	130	56	74	74
6.55	130	55	75	72
7	Digitalin (amorphous)		gr. $\frac{1}{50}$	
7.5	129	57	72	72
7.10	129	53	76	72
7.15	130	54	76	74
7.20	128	55	73	74
7.25	126	52	74	72
7.30	128	52	76	72
7.35	128	54	74	74
7.40	130	55	75	72
7.45	128	55	73	70
7.50	129	52	77	72
7.55	126	52	74	72
8	128	54	74	70
8.10	126	56	70	70
8.20	129	54	75	70
8.30	129	58	71	72

Digitoxin. Table III.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
3.30	126	64	62	74
3.50	128	64	64	74
4.5	128	66	62	74
4.20	128	65	63	72
4.26	Digitalin (crystalline) gr. $\frac{1}{250}$			
4.30	128	64	64	72
4.35	130	66	64	72
4.40	128	64	64	74
4.45	128	64	64	74
4.50	128	64	64	74
4.55	126	65	61	76
5	126	68	58	74
5.10	125	68	57	72
5.20	126	64	62	72
5.30	128	65	63	72
5.40	130	66	64	70
5.50	130	65	65	70
6	127	64	63	74
6.10	128	65	63	74
6.20	126	66	60	72
6.30	126	66	60	74

Digitoxin. Table IV.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
6.5	125	62	63	70
6.25	128	60	68	70
6.45	130	58	72	72
7.5	128	58	70	70
7.10	Digalen.	15 mins.		
7.15	128	60	68	70
7.20	128	60	68	68
7.25	130	60	70	68
7.30	128	64	64	68
7.35	128	62	66	70
7.40	127	62	65	70
7.45	126	60	66	70
7.50	126	60	66	68
7.55	128	58	70	70
8	126	62	64	72
8.10	128	65	63	68
8.20	128	63	65	70
8.30	130	60	70	70
8.40	126	62	64	68

Digitoxin. Table V.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
8.15	120	66	54	72
8.35	122	65	57	68
8.55	124	68	56	68
9.10	122	64	58	68
9.17	Digalen.	15 mins.		
9.20	124	62	62	70
9.25	122	64	58	68
9.30	122	64	58	68
9.35	120	66	54	68
9.40	120	65	55	68
9.45	120	65	55	70
9.50	122	65	57	70
9.55	124	62	62	68
10	124	62	62	72
10.10	122	65	57	70
10.20	120	64	56	70
10.30	123	62	61	68
10.40	121	62	59	68

Ergotoxine.

Ergotoxine was first isolated from ergot by Barger and Carr (Journal of Chem. Society, XCI., p.337). It is said to produce a prolonged contraction of the arterioles. According to Dale (Journal of Physiology, XXXIV, p.163) small doses cause vasoconstriction with a rise of blood pressure while large doses paralyse the myoneural junctions with the result that vasodilation occurs and the blood pressure falls.

The effect of ergotoxine on my blood pressure was investigated on four occasions. The preparation used was ergotoxine quinate, a soluble salt made by Burroughs, Wellcome, and Co. The makers informed me that this salt is not likely to decompose into ergotinine. Two series of observations were made on the effect of $\frac{1}{100}$ grain, and two series on the effect of $\frac{1}{50}$ grain, but in no case was the blood pressure or pulse rate appreciably affected.

The observations made are shown in the following tables:-

Ergotoxin. Table I.

Observations made on self before and after administration of ergotoxin gr $\frac{1}{100}$.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate Per Minute.
3.45	123	70	53	68
4.5	120	68	52	68
4.20	122	66	56	70
4.40	120	68	52	68
4.41	Ergotoxin gr $\frac{1}{100}$.			
4.43	120	70	50	68
4.45	121	69	52	66
4.50	120	69	51	68
4.55	119	69	50	68
5	118	71	47	68
5.5	122	70	50	66
5.10	121	71	50	66
5.15	120	72	48	64
5.22	118	68	50	66
5.25	120	66	54	68
5.30	122	68	54	68
5.35	122	70	52	70
5.40	120	70	50	68
5.45	121	68	53	68

Ergotoxin. Table II.

Observations made on self before and after administration of ergotoxin gr $\frac{1}{100}$.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
3.50	123	58	65	68
4.5	123	58	65	70
4.25	125	57	68	68
4.40	124	60	64	68
4.47	Ergotoxin gr $\frac{1}{100}$			
4.50	126	58	68	70
4.55	124	58	66	70
5	124	57	67	68
5.5	125	56	69	68
5.10	123	55	68	68
5.15	122	57	65	68
5.20	123	56	67	68
5.25	121	58	63	66
5.30	124	58	66	68
5.35	124	58	66	70
5.40	126	60	66	72
5.45	122	58	64	68
5.50	122	56	66	66

Ergotoxin. Table III

Observations made on self before and after administration of ergotoxin gr $\frac{1}{50}$.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate Per Minute.
6.15	126	56	70	68
6.35	128	60	68	68
6.55	128	60	68	70
7.15	128	57	71	72
7.17	Ergotoxin gr $\frac{1}{50}$.			
7.20	128	58	70	72
7.25	125	57	68	72
7.30	128	57	71	72
7.35	127	60	67	72
7.40	126	60	66	74
7.45	129	60	69	72
7.50	128	60	68	70
7.55	128	58	70	70
8.	128	58	70	68
8.5	125	56	69	70
8.10	126	58	68	70
8.20	128	58	70	72

Ergotoxin. Table IV.

Second series of observations made on self before and after administration of ergotoxin gr $\frac{1}{50}$.

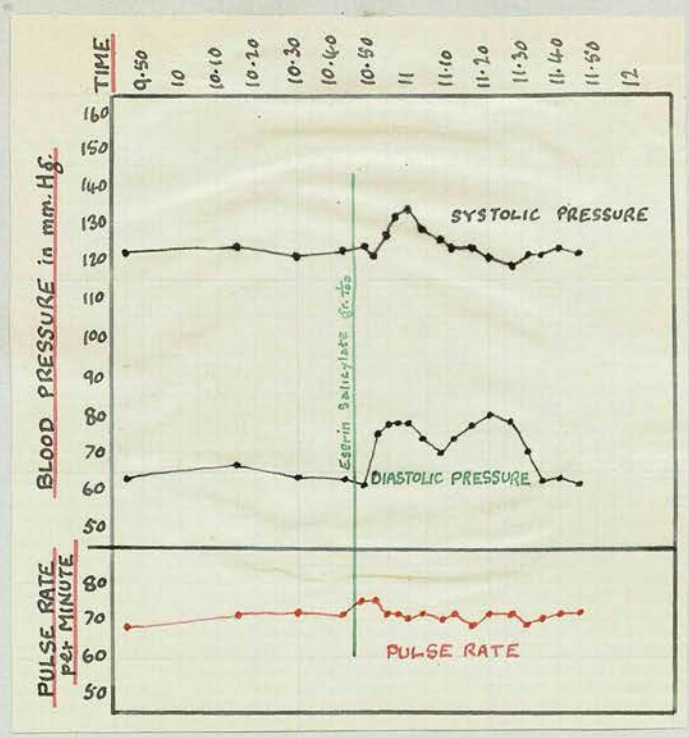
Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure	Pulse Rate Per Minute.
9.10	129	65	64	68
9.30	128	62	66	68
9.40	127	60	67	70
10	128	62	66	70
10.5	Ergotoxin gr $\frac{1}{50}$.			
10.7	128	64	64	70
10.10	126	64	62	70
10.15	126	62	64	70
10.20	128	62	66	68
10.25	128	62	66	72
10.30	125	60	65	72
10.35	128	60	68	70
10.40	130	62	68	74
10.45	128	60	68	70
10.50	126	60	66	68
10.55	126	64	62	68
11	126	62	64	68
11.5	129	60	69	70
11.10	126	60	66	68

Eserin.

Eserin is well known to act as a blood pressure elevator, but authorities are at variance as to how this effect is produced. Williams (Latham and English, System of Treatment, vol.I, p.1285) is the only recent writer whom I have found recommending this drug as a remedy for hypotension. He states that, administered hypodermically, it is of value in emergencies.

Three series of observations were made on the effect of eserin on my blood pressure. The preparation used was eserin salicylate (U.S.P.): the effect of $\frac{1}{100}$ grain was investigated on two occasions and the effect of $\frac{1}{50}$ grain on one occasion. The effect of each dose was to cause a transitory elevation of the systolic pressure, and a rather more persistent elevation of the diastolic pressure. The pulse rate remained unaltered, and the force of the cardiac contraction was never appreciably increased. Vomiting was induced on each occasion.

The first series of observations were made on the effect of $\frac{1}{100}$ grain of eserin salicylate. The effect of this dose on the blood pressure and pulse rate is shown by the following chart:-



The systolic pressure began to rise 5-7 minutes after the drug was administered, and remained elevated for 11-17 minutes; the highest point it reached (133 mm. Hg.) being 10.5 mm. Hg. higher than the average systolic pressure observed before the experiment commenced. The diastolic pressure began to rise in 2-5 minutes, and remained elevated for 40 - 47 minutes; the highest point reached (80 mm. Hg.) being 15.5 mm. Hg. higher than the average diastolic pressure observed before the experiment commenced.

A sensation of nausea was first noticeable in about 25 minutes. It got gradually worse, and sweating and a sensation of general weakness followed. Vomiting occurred about 40 minutes after the drug was administered.

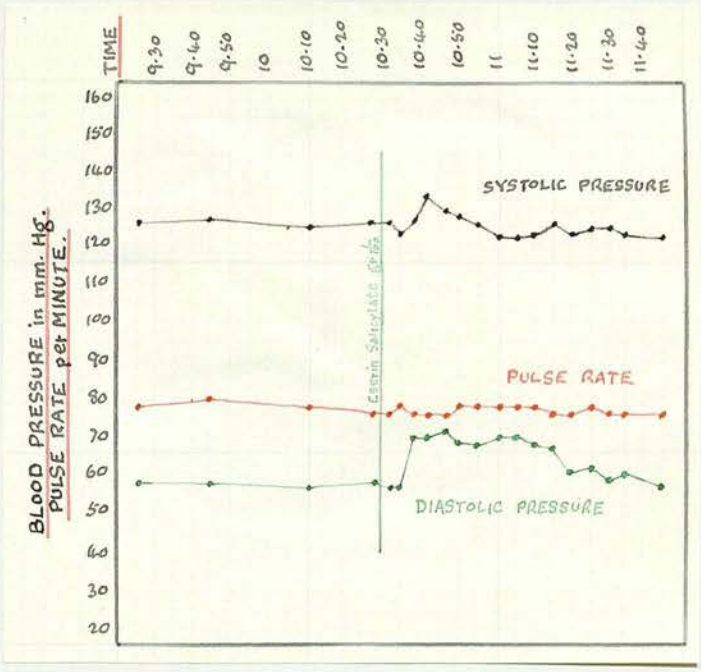
Details of the observations made are given in the following table:-

Eserin/

Eserin. Table I.

Time P.M.	Systolic Pressure in mm. Hg.	Diastolic Pressure in mm. Hg.	Pulse Pressure	Pulse Rate per Minute.	
9.45	122	63	59	68	
10.15	124	67	57	72	
10.30	121	64	57	72	
10.43	123	64	59	72	
10.46	Eserin	Salicylate	gr. $\frac{1}{100}$		
10.48	124	62	62	76	
10.51	121	75	46	76	
10.53	126	77	49	72	
10.56	132	77	55	72	
11	133	77	56	70	
11.4	127	74	53	72	
11.8	125	70	55	70	Nausea.
11.12	124	74	50	72	
11.16	124	77	47	68	
11.20	120	80	40	72	
11.27	119	79	40	72	Vomited twice.
11.31	121	70	51	68	
11.35	121	62	59	70	
11.40	124	63	61	72	
11.45	123	61	62	72	

A second series of observations on the effect of $\frac{1}{100}$ grain of eserin salicylate were made three days after those just recorded. The following chart shows how the blood pressure was affected in this experiment:-



The height and persistence of the elevation of the systolic and diastolic pressures in this case will be seen to be very similar to those observed in the first experiment. Vomiting on this occasion occurred about 47 minutes after the administration of the drug.

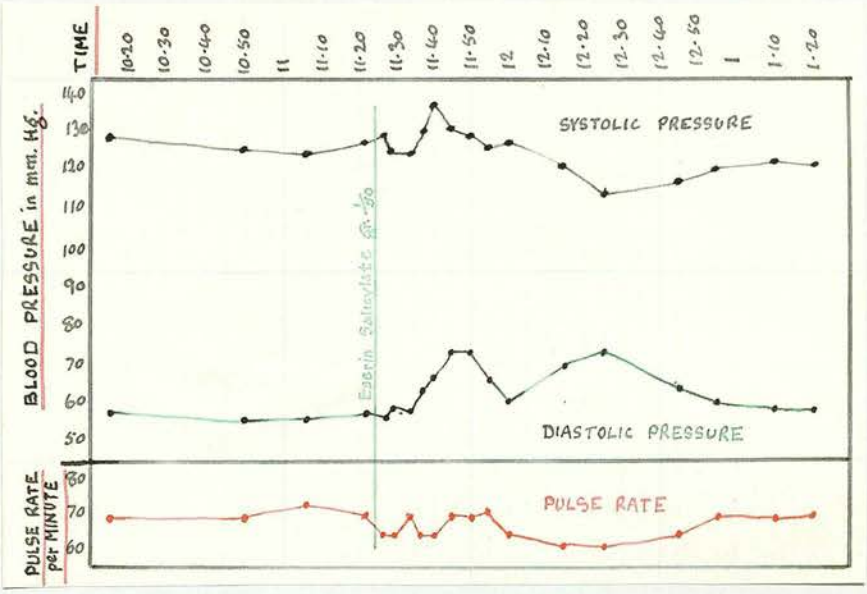
The observations made are shown in detail in the following table.

Eserin/

Eserin. Table II.

Time P.M.	Systolic Pressure in mm. Hg.	Diastolic Pressure in mm. Hg.	Pulse Pressure.	Pulse Rate per Minute	
9.25	126	57	69	78	
9.45	127	57	70	80	
10.10	125	56	69	78	
10.27	126	57	69	76	
10.30	Eserin Salicylate	gr. $\frac{1}{100}$			
10.32	126	56	70	76	
10.35	124	56	68	78	
10.38	127	70	57	76	
10.42	134	70	64	76	
10.46	130	72	58	76	
10.50	129	69	60	78	
10.55	126	68	58	78	
11	123	70	53	78	Nausea
11.5	123	70	53	78	
11.10	124	68	56	78	
11.15	126	66	60	76	
11.20	124	60	64	76	Vomited once.
11.25	125	62	63	78	
11.30	125	59	66	76	
11.35	124	60	64	76	
11.45	123	56	67	76	

The third series of observations were made on the effect of $\frac{1}{50}$ grain of eserin salicylate. The following chart shows the effect of this dose on the blood pressure and pulse rate:-



The systolic pressure began to rise 9 - 12 minutes after the drug was administered, and remained elevated for about 15 - 20 minutes; the highest point it reached (137 mm. Hg.) being 11.5 mm. Hg. higher than the average systolic pressure observed before the experiment commenced. It then fell considerably, and 61 minutes after the administration of the drug it was 11.5 mm. Hg. lower than the average pressure observed before the experiment was begun; after this it again began to rise, but was still somewhat low when the observations were discontinued 45 minutes later. The diastolic pressure began to rise in 9 - 12 minutes, and remained elevated for about 70 - 80 minutes; the highest point it reached (74 mm. Hg.) being 13.25 mm. Hg. higher than the average/

average diastolic pressure observed before the experiment commenced. The diastolic pressure fell considerably just before vomiting occurred, but again rose for a time afterwards.

A sensation of faintness was noted about 10 minutes after the drug was administered; this persisted until vomiting occurred, and for a short time afterwards. Nausea and sweating came on shortly after the faintness was noted. The faintness and nausea increased until I felt almost too ill to continue the observations. Violent vomiting and a motion of the bowels occurred between 35 and 50 minutes after the eserin was administered, after this improvement in the general condition was fairly rapid.

The observations made in this experiment are shown in the following table:-

Eserin Table III.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.	
10.15	128	57	71	68	
10.50	125	55	70	68	
11.5	124	55	69	72	
11.22	125	56	69	68	
11.24	Eserin Salicylate gr. $\frac{1}{50}$				
11.26	128	56	72	64	
11.29	124	58	66	64	
11.33	124	58	66	68	Faintness.
11.36	130	64	66	64	
11.40	137	67	70	64	Nausea.
11.45	130	74	56	68	
11.50	128	74	54	68	
11.55	125	66	59	70	
12	126	60	66	64	Vomited several times. Bowels opened once.
12.15	120	72	48	60	
12.25	114	74	40	60	
12.45	116	64	52	64	
12.55	120	60	60	68	
1.10	122	58	64	68	
1.20	121	58	63	68	

Pituitary Extract.

Extract of the posterior lobe of the pituitary body is at present much used as a blood pressure elevator, and several clinical reports of its value have been published in recent years.

Cow (Proceedings of the Royal Society of Medicine, 1911, vol.IV. part III, Pharmacological Section pp.86-89) has shown that pituitary extract does not have the same action on all vessels. He found that although it constricted the systemic arteries it dilated the splanchnics. He says, "Since pituitary extract produces a general increase in blood pressure in the intact animal, it follows that, caeteris paribus, the constricting effect on the systemic vessels generally must outweigh the dilating effect on the splanchnic vessels, a theory which my experiments do not suggest, or else we must believe that pituitary extract has a central action which may tend to hold in check the local dilating effect on the splanchnic vessels, or possess both a dilating element and a constricting element of which either the one or the other may predominate on different occasions".

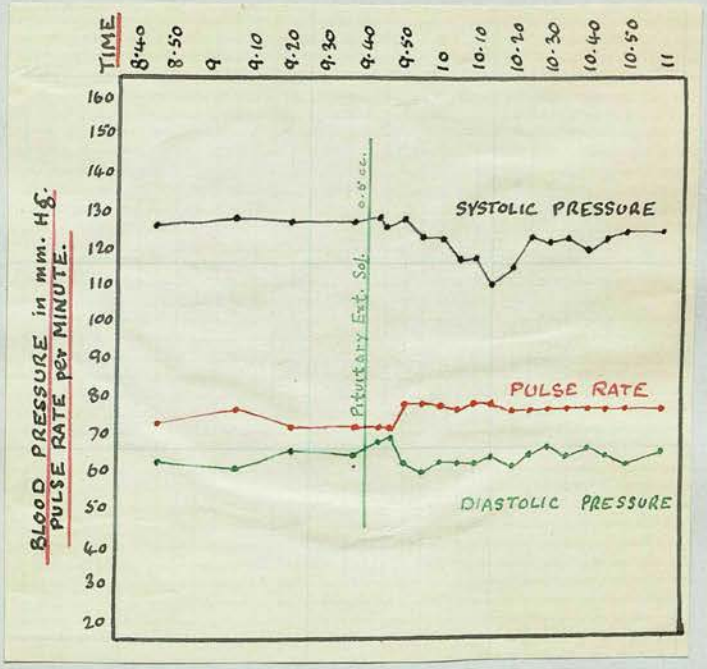
Five series of observations were made on the effect of pituitary extract. The preparation used was the sterilised 20% solution made by Burroughs, Wellcome, & Co. Four series of observations were made on the effect of the drug on my own blood pressure; one series on the effect of 0.5 cc of the 20% solution; one series

on/

on the effect of 2 cc; and two separate series on the effect of 1 cc. One series of observations were also made on the effect of 1 cc. on a female subject, age 36, who had an abnormally low blood pressure.

When administered to myself the drug on each occasion caused a considerable fall of the systolic pressure, while the diastolic pressure and pulse rate remained unaffected. A motion of the bowels occurred within half an hour of the administration of 1 cc. and 2 cc. doses, but even with the largest dose no unusual sensations were experienced. In the case of the female subject the drug was not observed to have any appreciable effect.

The following chart shows the effect of 0.5 cc. on my blood pressure:-



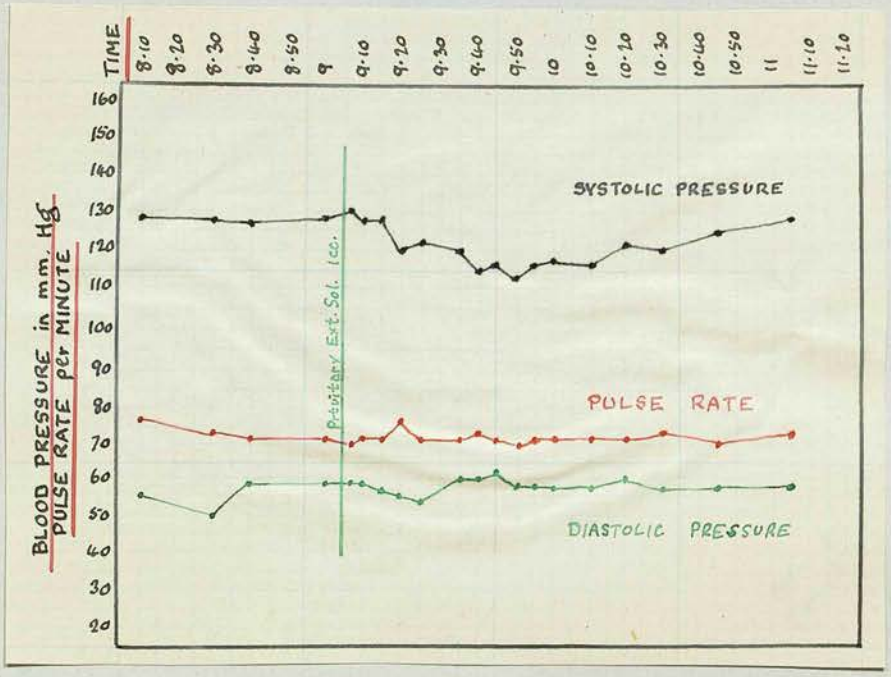
The systolic pressure began to fall 20-25 minutes after the drug was administered and remained low for about 20 minutes. The lowest point observed (110 mm. Hg.) was reached 35 minutes after the drug was administered, and was 17.25 mm. Hg. lower than the average systolic pressure observed before the experiment commenced.

The observations made in this experiment are shown in the following table:-

Pituitary Extract. Table I.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate Per Minute.
8.45	126	63	63	74
9.5	129	62	67	76
9.20	127	65	62	72
9.36	127	64	63	72
9.40	Pituitary extract sol. 0.5 cc.			
9.43	129	66	63	72
9.45	126	68	58	72
9.50	129	62	67	78
9.55	124	60	64	78
10.	124	62	62	78
10.5	117	62	55	76
10.10	118	62	56	78
10.15	110	63	47	78
10.20	115	62	53	76
10.25	124	64	60	76
10.30	123	65	58	76
10.35	124	64	60	76
10.40	120	65	55	76
10.45	124	64	60	76
10.50	125	62	63	76
11.	125	64	61	76

The effect of 1 cc of pituitary extract solution on my blood pressure is shown by the following chart:-



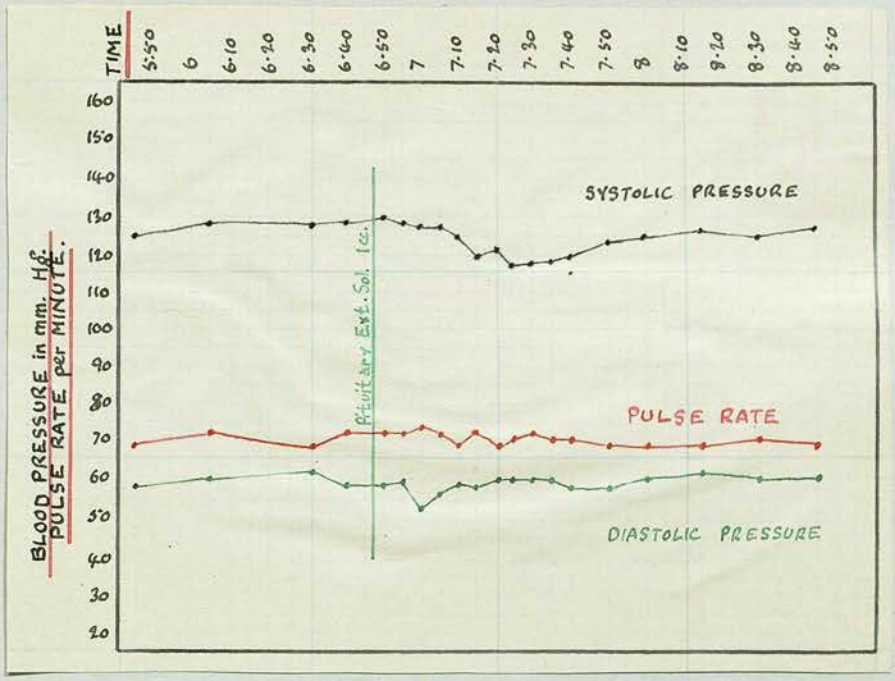
The systolic pressure began to fall in about 15 minutes and remained low for about 80 minutes. The lowest point observed (114 mm. Hg.) was 14.25 mm. Hg. lower than the average systolic pressure observed before the experiment commenced. A motion of the bowels occurred about 25 minutes after the drug was administered.

The observations made in this experiment are given in the following table:-

Pituitary Extract. Table II.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate Per Minute.	
8.10	129	55	74	76	
8.30	128	50	72	74	
8.40	127	58	69	72	
9.	129	58	71	72	
9.5	Pituitary extract sol. 1 cc.				
9.7	130	58	72	70	
9.10	129	58	71	72	
9.15	129	57	72	72	
9.20	120	55	65	76	
9.25	122	54	68	72	Bowels opened once.
9.35	120	60	60	72	
9.40	115	60	55	74	
9.45	116	62	54	72	
9.50	114	58	56	70	
9.55	116	58	58	72	
10.	117	58	59	72	
10.10	116	58	58	72	
10.20	122	60	62	72	
10.30	120	58	62	74	
10.45	125	58	67	70	
11.5	128	58	70	74	

A second series of observations were made on the effect of 1 cc. pituitary solution. The following chart shows the effect on the blood pressure on this occasion:-



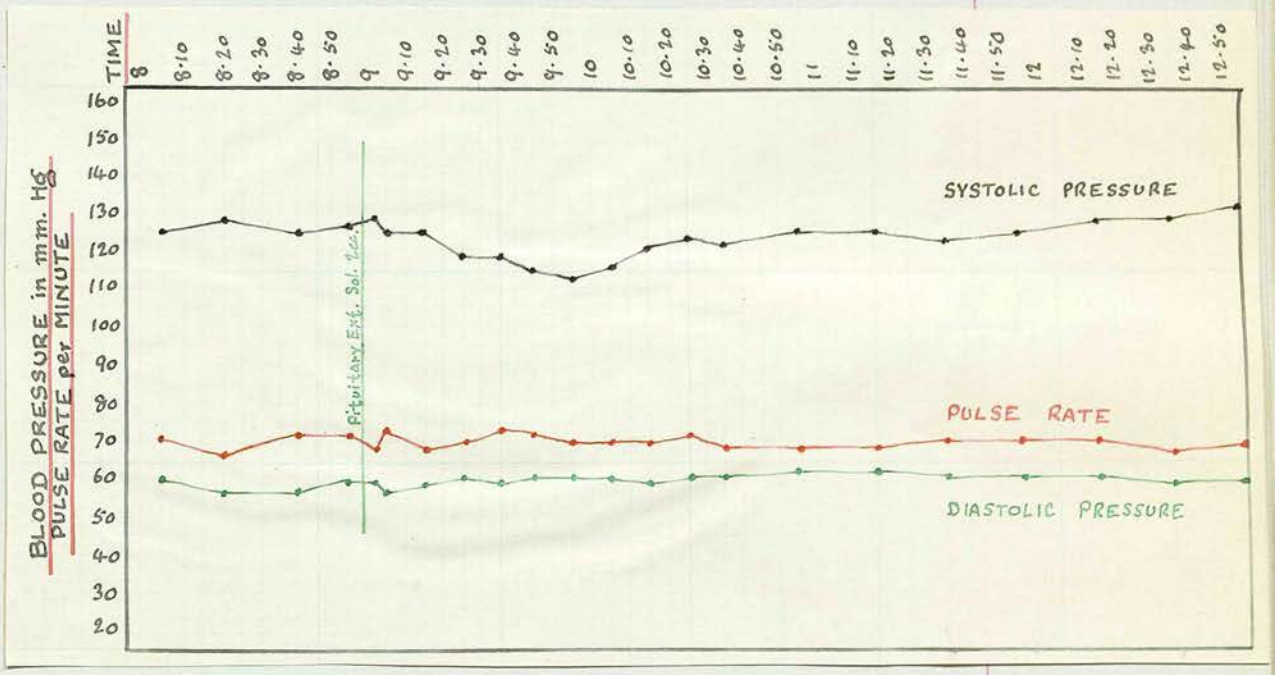
The systolic pressure began to fall about 25 minutes after the drug was administered and remained low for about half an hour. The lowest point observed (116 mm.Hg.) was reached in 38 minutes, and was 11.75 mm. Hg. lower than the average systolic pressure observed before the experiment commenced. A motion of the bowels occurred about half an hour after the drug was administered.

The observations made in this experiment are given in the following table:-

Pituitary Extract. Table III.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate Per Minute.	
5.45	125	58	67	68	
6.5	129	60	69	72	
6.30	128	62	66	68	
6.40	129	58	71	72	
6.47	Pituitary extract sol. 1 cc.				
6.50	130	58	72	72	
6.55	129	59	70	72	
7	128	53	75	74	
7.5	128	57	71	72	
7.10	125	59	66	68	
7.15	120	58	62	72	Bowels opened once.
7.20	122	60	62	68	
7.25	116	60	56	70	
7.30	117	60	57	72	
7.35	118	60	58	70	
7.40	120	58	62	70	
7.50	124	58	66	68	
8.	125	60	65	68	
8.15	127	62	65	68	
8.30	125	60	65	70	
8.45	127	60	67	68	

The effect of 2 cc. of pituitary extract solution on my blood pressure was investigated one one occasion. Observations were made at frequent intervals for a period of four hours after the drug was administered. The following chart shows the effect of this dose:-



The systolic pressure began to fall about 20-25 minutes after the drug was administered and it remained low for about an hour. The lowest point observed (114 mm. Hg.) was reached in 57 minutes and was 12.25 mm. Hg. lower than the average systolic pressure observed before the experiment commenced.

An easy motion of the bowels occurred about 20 minutes after the drug was administered.

The observations made in this experiment are shown in the following table:-

Pituitary Extract. Table IV.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate Per Minute.	
8.5	125	60	65	72	
8.20	128	56	72	68	
8.40	125	56	69	72	
8.55	127	58	69	72	
8.58	Pituitary extract sol. 2 cc.				
9.1	128	58	70	68	
9.5	125	56	69	74	
9.15	125	58	67	68	Bowels opened once.
9.25	117	60	57	70	
9.35	118	58	60	74	
9.45	115	60	55	72	
9.55	114	60	54	70	
10.5	118	60	58	70	
10.15	121	58	63	70	
10.25	124	60	64	72	
10.35	122	60	62	68	
10.55	125	62	63	68	
11.15	125	62	63	66	
11.35	122	60	62	70	
11.55	125	60	65	70	
12.15	128	60	68	70	
12.35	128	58	70	66	
12.55	132	58	74	68	

The following table shows the effect of 1 cc. pituitary extract solution on the blood pressure and pulse rate of M.S., a female subject, age 36.

Pituitary Extract. Table V.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
7.45	94	48	46	80
8	98	48	50	80
8.15	98	52	46	78
8.30	93	48	45	78
8.37	Pituitary Extract sol. 1 cc.			
8.41	95	48	47	82
8.45	92	53	39	80
8.50	95	49	46	80
8.55	95	49	46	80
9	98	47	51	80
9.5	97	54	43	76
9.10	98	49	49	76
9.15	99	48	51	78
9.20	96	48	48	80
9.25	98	52	46	80
9.30	96	48	48	80
9.35	94	48	46	78
9.40	94	50	44	76

So many experimental and clinical reports of the value of pituitary extract as a blood pressure elevator have been published in recent years that its effect in my experiments was rather surprising.

It would seem that either, as suggested by Cow (loc. cit.) pituitary extract must possess both a dilating element and a constricting element of which either the one or the other may predominate on different occasions; or else the explanation may possibly be that in cases of hypotension the splanchnic vessels are already more or less fully dilated, and in marked cases cannot be further dilated by the drug, so that the action of pituitary extract on the vessels in such cases is restricted to the systemic arteries which become constricted, and the blood pressure consequently rises somewhat. In cases of moderate hypotension the splanchnic vessels are probably not fully dilated, and hence can be further dilated by the drug, but the constriction of the systemic arteries may be just about sufficient to compensate for this extra dilatation with the result that little or no change in the systolic pressure is obtained. On the other hand, in a person whose arterial tension is normal, the constriction of the systemic arteries produced by a dose of pituitary extract is probably insufficient to compensate for the simultaneous dilatation of the splanchnic arteries, as Cow's experiments seemed to indicate, and the systolic pressure falls.

Strychnine.

The value of strychnine as a blood pressure elevator has recently been disputed. Hirschfelder (Diseases of Heart and Aorta, 1913, p.251) states that he has injected as much as $\frac{1}{4}$ grain hypodermically without observing any effect on the blood pressure or pulse rate. McKenzie (Diseases of the Heart, 1913, p.354) considers it to be absolutely without detectable effect on the heart or blood-vessels of the human subject. Price (Clinical Journal, Aug. 28th, 1912, p.335) considers it valueless as a blood pressure elevator. On the other hand Cook and Briggs (John Hopkins' Hospital Reports, 1903, vol.XI., p.512) consider strychnine to be one of the most effective pressor drugs, and state that in doses of $\frac{1}{60}$ - $\frac{1}{10}$ grain it produces an elevation of the systolic pressure lasting from one to four hours. Edgecombe (Practitioner, April, 1911, p.532) concludes from his observations that it "exerts something of a sustained pressor effect".

I made four series of observations on the effect of this drug, the hydrochloride of strychnine being used. The effect of $\frac{1}{15}$ grain on my blood pressure was investigated on one occasion, and the effect of $\frac{1}{10}$ grain on two occasions. The effect of $\frac{1}{15}$ grain was also investigated once on another healthy male subject. In no case was the strychnine observed to have any definite/

definite effect on the systolic or diastolic pressure; the pulse rate was slightly accelerated on one occasion after the administration of $\frac{1}{10}$ grain, but was unaffected by the other doses investigated.

The observations made are shown in the following tables:-

Strychnine. Table I.

Observations made on self before and after administration of strychnine hydrochloride gr. $\frac{1}{15}$

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure	Pulse Rate Per Minute.
5.10	121	64	57	78
5.25	122	60	62	76
5.45	123	62	61	74
6.1	122	64	58	76
6.3	Strychnine hydrochloride gr. $\frac{1}{15}$			
6.5	121	64	57	76
6.10	118	62	56	76
6.15	121	62	59	78
6.20	123	64	59	76
6.26	127	64	63	76
6.33	126	62	64	74
6.38	123	63	60	78
6.45	121	64	57	74
6.56	118	66	52	72
7.5	120	64	56	76
7.10	123	64	59	74
7.15	123	63	60	76

Strychnine Table II.

Observations made on self before and after administration of strychnine hydrochloride gr. $\frac{1}{10}$.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure	Pulse Rate Per Minute.
10.45	124	62	62	64
11.15	121	64	57	64
11.30	123	62	61	62
* 11.45	123	63	60	64
11.47	Strychnine hydrochloride gr. $\frac{1}{10}$			
11.49	123	66	57	60
11.53	123	66	57	64
11.57	122	65	57	68
12.2	123	64	59	68
12.7	122	65	57	72
12.14	121	63	58	70
12.25	124	62	62	72
12.36	126	64	62	70
12.49	124	63	61	70
12.55	124	64	60	70
1.5	122	64	58	70
1.15	124	62	62	68

Strychnine Table III.

Observations made on self before and after administration of strychnine hydrochloride gr.$\frac{1}{10}$.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate Per Minute.
12.15	124	62	62	70
12.40	127	60	67	76
12.50	127	62	65	72
12.55	126	62	64	72
12.57	Strychnine hydrochloride gr.$\frac{1}{10}$			
1	128	64	64	68
1.5	126	62	64	68
1.10	128	62	66	70
1.15	125	63	62	68
1.25	126	60	66	66
1.35	128	62	66	64
1.45	126	66	60	66
1.52	126	64	62	66
2.5	124	64	60	68
2.10	124	62	62	68
2.15	126	62	64	68
2.20	125	64	61	70

Strychnine Table IV.

Observations made on W.W. healthy male subject, age 24, before and after administration of strychnine hydrochloride gr. $\frac{1}{15}$.

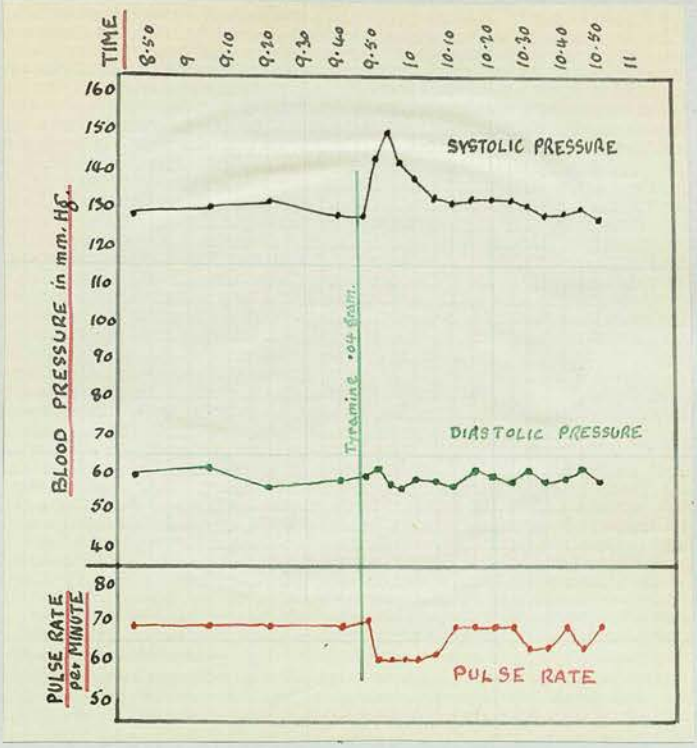
Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate Per Minute.
9.10	128	67	61	76
9.30	130	68	62	76
9.45	128	68	60	74
10.10	127	68	59	76
10.15	Strychnine hydrochloride gr $\frac{1}{15}$			
10.17	128	68	60	74
10.20	128	67	61	74
10.25	128	69	59	76
10.30	127	68	59	76
10.35	126	68	58	76
10.40	128	68	60	78
10.45	128	67	61	78
10.50	125	66	59	80
10.55	128	68	60	76
11.	128	70	58	76
11.5	126	70	56	74
11.15	126	68	58	78
11.20	128	66	62	78

Tyramine.

Tyramine (para-hydroxyphenylethylamine) is an organic base produced by the action of certain ferments on tyrosine. It is said to be the most important active constituent of watery extracts of ergot from which it was first isolated by Dale (Journal of Physiology, XXXIX., p.25). Its physiological action is said to differ from that of adrenalin mainly in being slower in onset and weaker, though more prolonged (Fortescue-Brickdale, Guide to the Newer Remedies, 1910, p.131).

Five series of observations were made on the effect of this drug on my blood pressure. One series was made on the effect of .04 gram, two series were made on the effect of .06 gram, and two series on the effect of .08 gram. One series on the effect of .06 gram was also made on another healthy made subject. In every case a considerable and rapid elevation of the systolic pressure occurred, but the diastolic pressure was never definitely affected. The pulse rate was slowed for a short time on five occasions. Slight palpitation was felt for a few minutes on two occasions after the drug had been administered, but otherwise no unusual sensations were experienced.

The following chart shows the effect of .04 gram tyramine on my blood pressure and pulse rate:-



The systolic pressure was elevated 3-5 minutes after the drug had been administered. It remained elevated for 10 - 15 minutes. The maximum height (150 mm. Hg.) was attained in 8 minutes, and was 20.5 mm. Hg. higher than the average systolic pressure observed before the experiment commenced. The diastolic pressure remained unaffected. The pulse rate was somewhat slowed about 5 minutes after the drug had been administered, and it remained so for 15 - 20 minutes.

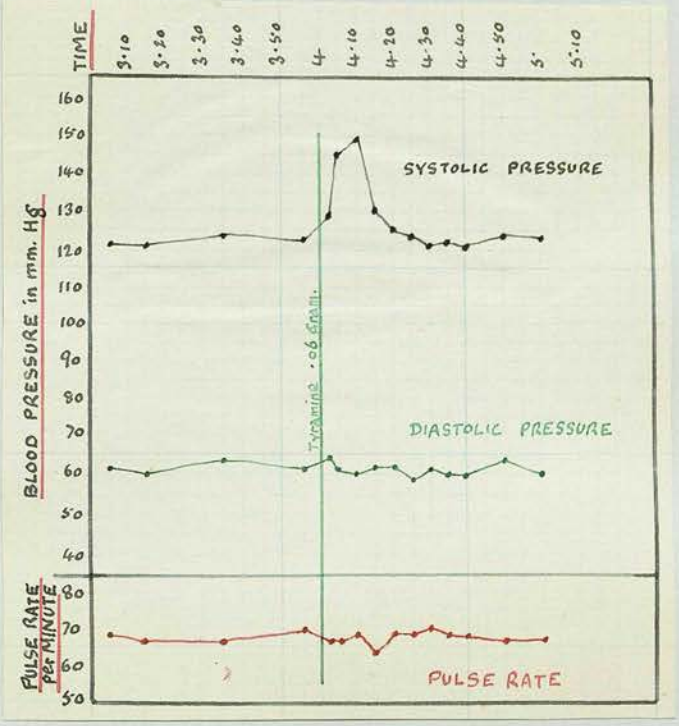
The observations made in this experiment are shown in the following table:-

Tyramine. Table I./

Tyramine. Table I.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
8.45	128	60	68	68
9.5	130	62	68	68
9.20	131	56	75	68
9.40	129	58	61	68
9.45	Tyramine	.04 grm.		
9.47	129	60	69	70
9.50	144	62	82	60
9.53	150	57	93	60
9.56	143	56	87	60
10	138	58	80	60
10.5	133	58	75	62
10.10	132	57	75	68
10.15	133	62	71	68
10.20	133	60	73	68
10.25	133	58	75	68
10.30	131	62	69	64
10.35	128	58	70	64
10.40	129	59	70	68
10.45	130	62	68	64
10.50	127	58	69	68

The following chart shows the effect of .06 grm. tyramine on my blood pressure and pulse rate:-



The systolic pressure was elevated about 3 minutes after the drug had been administered, and it remained elevated for 12 - 15 minutes. The maximum height (149 mm.Hg.) was attained in 10 minutes, and was 26.5 mm. Hg. higher than the average systolic pressure observed before the experiment commenced. The diastolic pressure and pulse rate were not appreciably affected.

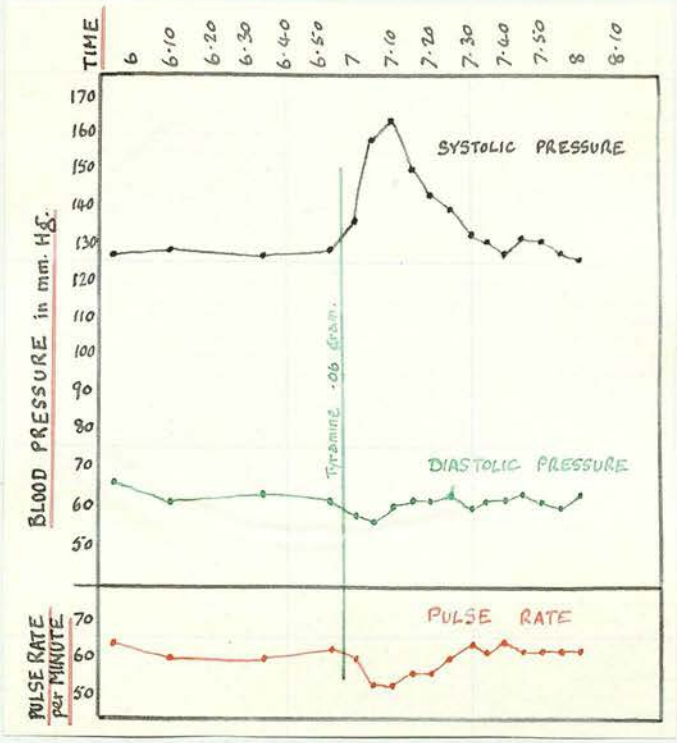
The observations made in this experiment are shown in the following table:-

Tyramine. Table II./

Tyramine. Table II.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
3.5	122	62	60	68
3.15	121	60	61	66
3.35	124	64	60	66
3.55	123	62	61	70
4	Tyramine .06 grm.			
4.3	129	64	65	66
4.5	145	62	83	66
4.10	149	60	89	68
4.15	130	62	68	64
4.20	125	62	63	68
4.25	124	58	66	68
4.30	122	62	60	70
4.35	123	60	63	68
4.40	122	60	62	68
4.50	124	64	60	66
5	124	60	64	66

The following chart shows the effect of another dose of .06 gram of tyramine on my blood pressure and pulse rate:-



The systolic pressure was considerably elevated three minutes after the drug had been administered and it remained high for 35 - 40 minutes. The maximum height (164 mm. Hg.) was attained in 13 minutes and was 36.25 mm. Hg. higher than the average systolic pressure observed before the experiment commenced. The diastolic pressure was not definitely affected. The pulse rate was slowed 5 - 8 minutes after the drug had been administered and it remained somewhat slow for 15 - 20 minutes.

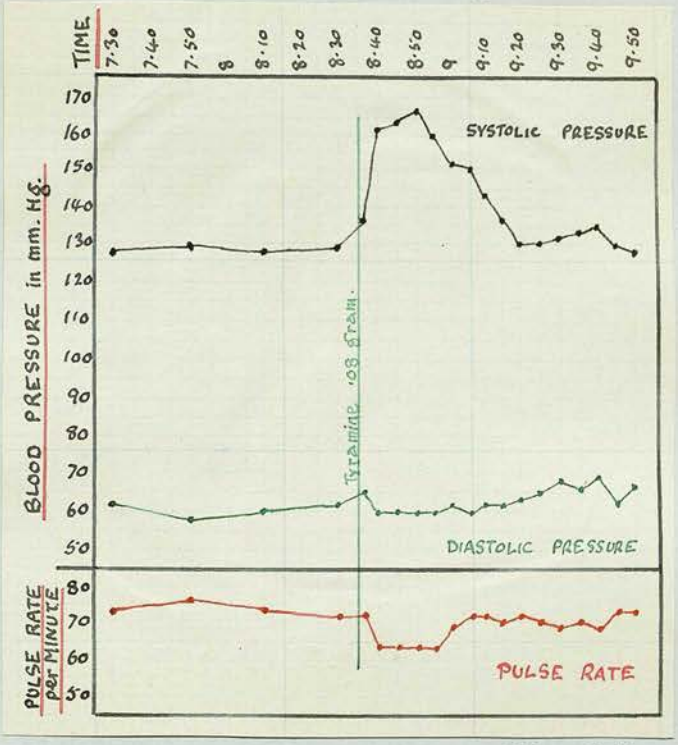
The observations made in this experiment are shown in the following table:-

Tyramine. Table III./

Tyramine. Table III.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
5.55	127	66	61	64
6.10	129	62	67	60
6.35	126	64	62	60
6.53	129	62	67	62
6.57	Tyramine	.06 gram.		
7	137	58	79	60
7.5	159	56	103	54
7.10	164	60	104	54
7.15	150	62	88	56
7.20	144	62	82	56
7.25	140	63	77	60
7.30	134	60	74	64
7.35	132	62	70	62
7.40	128	62	66	64
7.45	133	64	69	62
7.50	132	62	70	62
7.55	128	60	68	62
8	126	64	62	62

The next chart shows the effect of .8 gram. of tyramine on by blood pressure and pulse rate:-



The systolic pressure was considerably elevated two minutes after the drug had been administered, and it remained elevated for about 40 minutes. The highest point (166 mm. Hg.) was reached in 15 minutes, and was 38 mm. Hg. higher than the average systolic pressure observed before the experiment commenced. The diastolic pressure remained unaffected. The pulse rate was slowed about 5 minutes after the drug was administered and remained slow for about 20 minutes. Slight palpitation was noticed about 10 minutes after the drug was administered, it had completely passed off 6 minutes later.

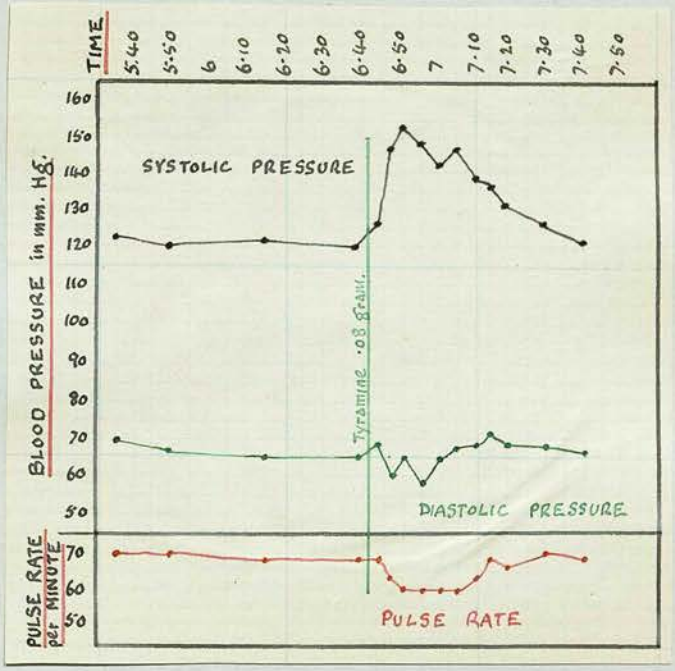
The observations made in this experiment are shown in the following table:-

Tyramine. Table IV./

Tyramine. Table IV.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
7.30	127	62	65	74
7.50	129	58	71	76
8.10	127	60	67	74
8.30	129	61	68	72
8.35	Tyramine	.08 grm.		
8.37	136	65	71	72
8.40	162	60	102	64
8.45	164	60	104	64
8.50	166	60	106	64
8.55	160	60	100	64
9	152	62	90	68
9.5	150	60	90	72
9.10	144	62	82	72
9.15	136	62	74	70
9.20	130	64	66	72
9.25	130	65	65	70
9.30	132	68	64	68
9.35	134	67	67	70
9.40	135	69	66	68
9.45	130	63	67	74
9.50	129	66	63	74

The following chart shows the effect of .08 gram of tyramine on my blood pressure and pulse rate on another occasion:-



The systolic pressure was elevated 3 - 5 minutes after the drug had been administered and remained high for 45 - 50 minutes. The highest point (153 mm. Hg.) was reached in 9 minutes and was 31.75 mm. Hg. higher than the average systolic pressure observed before the experiment commenced. The diastolic pressure remained unaffected, but the pulse was slowed about 5 minutes after the drug had been administered and remained somewhat slow for about 25 minutes. No palpitation was noticed on this occasion.

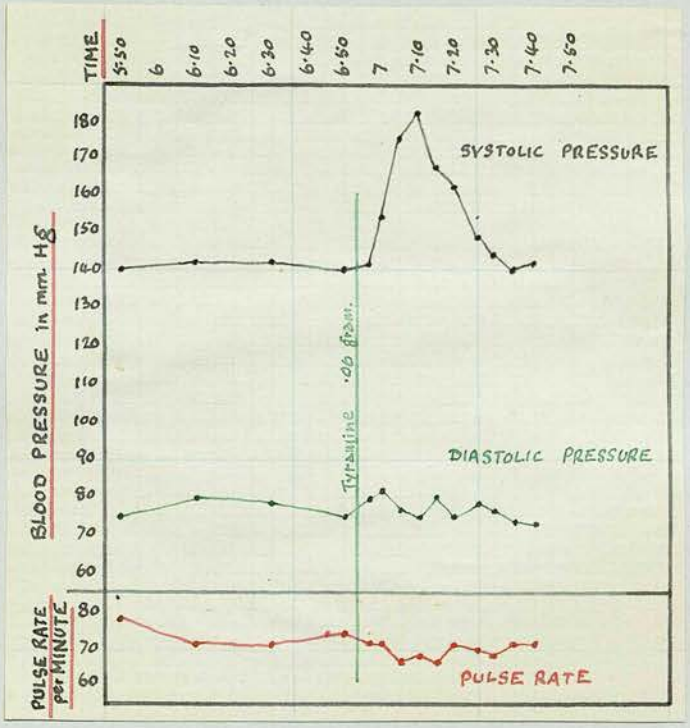
The observations made in this experiment are shown in the following table:-

Tyramine. Table V./

Tyramine. Table V.

Time P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
5.35	123	70	53	70
5.50	120	66	54	70
6.15	122	65	57	68
6.38	120	65	55	68
6.41	Tyramine	.08 gram.		
6.43	127	68	59	68
6.46	147	60	87	64
6.50	153	65	88	60
6.55	149	58	91	60
7	142	65	77	60
7.5	146	68	78	60
7.10	138	69	69	64
7.15	136	71	65	68
7.20	131	69	62	66
7.30	126	68	58	70
7.40	122	66	56	68

The following chart shows the effect of .6 gram of tyramine on the blood pressure and pulse rate of G.H., a healthy male subject, age 32.



This subject's systolic pressure was elevated 4 - 7 minutes after the drug had been administered and remained high for 25 - 30 minutes. The maximum height (182 mm. Hg.) was attained in 17 minutes and was 41 mm. Hg. higher than his average systolic pressure observed before the experiment commenced. The diastolic pressure was unaffected. The pulse rate was slightly slowed 8 - 12 minutes after the drug had been administered and it remained rather slow for 10 - 15 minutes. Slight palpitation was complained of about 10 minutes after the drug had been administered, it lasted for about 5 minutes.

The observations made in this experiment are shown in the following table:-

Tyramine. Table VI./

Tyramine. Table VI.

Time. P.M.	Systolic Pressure in mm.Hg.	Diastolic Pressure in mm.Hg.	Pulse Pressure.	Pulse Rate per Minute.
5.50	140	75	65	76
6.10	142	80	62	72
6.30	142	78	64	72
6.50	140	75	65	74
6.53	Tyramine	.06 gram.		
6.56	141	80	61	72
7	154	81	73	72
7.5	175	77	98	66
7.10	182	75	107	68
7.15	166	80	86	66
7.20	162	75	87	72
7.25	148	78	70	70
7.30	144	76	68	68
7.35	140	74	66	72
7.40	142	74	68	72

CONCLUSIONS.

The physiological and pharmacological action of drugs are not necessarily similar and for this reason some of the conclusions arrived at from those investigations may be considered of doubtful value. I venture to suggest however, that, until the condition of the vessels in cases of hypotension has been definitely determined, it is only by observing the effect of drugs on healthy individuals that a correct estimation of their possible value as blood pressure elevators in cases of hypotension can be formed. Observations made on the effect of drugs on the blood pressure of patients suffering from marked hypotension seem to me to be unreliable, as the blood pressure in such cases is often readily influenced by a number of causes other than the drugs administered, and in serious cases medicinal treatment is seldom the only means by which the physician endeavours to improve a patient's condition.

With the exception of adrenalin, eserin, pituitary extract, and tyramine, the drugs used in my experiments were found to have no appreciable effect on the blood pressure, and I am of the opinion that they are probably of no value as blood pressure elevators.

Pituitary extract was found to have no effect on the blood pressure of one subject whose arterial tension/

tension was abnormally low, and to lower my own systolic pressure, no rise occurring even on one occasion when observations were continued for four hours after a large dose had been administered. I have already suggested that, for certain reasons, its effect in cases of marked hypotension might be different, but I consider it of very doubtful value.

Eserin was found to elevate both the systolic and diastolic pressure. It caused distressing nausea, vomiting, and faintness however, and for this reason its use as a blood pressure elevator does not seem to be advisable.

Adrenalin produced a marked elevation of the systolic pressure and an even more marked depression of the diastolic pressure. It also caused faintness, tremulousness, and palpitation. I have suggested that the effect of this drug may be possibly due to its causing a temporary aortic regurgitation. It seems to be a dangerous drug which should be used with great caution.

Tyramine was found to elevate the systolic pressure very powerfully. It did not appreciably affect the diastolic pressure and, except for slight, transitory palpitation on two occasions, it caused no unpleasant symptoms. The effect on the systolic pressure was apparent in from 2 to 7 minutes and lasted for from 10 to 50 minutes. Its local effect on the vessels at the site of injection was not nearly so marked as

that/

that of adrenalin, but as a blood pressure elevator it appeared to be a greatly superior drug. I consider it to be a safe and effective blood pressure elevator, and think that injected hypodermically or intravenously it should prove of great value in emergencies.

SUMMARY.

Investigations were made to determine what immediate effect certain drugs supposed to act as blood pressure elevators have on the systolic and diastolic pressure of healthy individuals, the majority of the observations being made on the same subject.

The drugs were administered hypodermically and series of observations on the blood pressure and pulse rate were made for an hour or more afterwards. The investigations were all made in as nearly identical conditions as practicable, and care was taken to exclude anything but the drug administered from affecting the blood pressure.

Adrenalin. Four series of observations were made on the effect of 10 m. of a 1 in 1000 solution of adrenalin. It acted very rapidly on both the systolic and diastolic pressure; the former was elevated and the latter depressed. Faintness, tremulousness, palpitation, and abnormally deep respirations were caused by the drug.

It was suggested that the effect of adrenalin might be due to its producing a temporary aortic regurgitation, and the conclusion arrived at was that it was a dangerous drug, which should be used with caution.

Atropine. Three series of observations were made on the effect of atropine sulphate in doses of $\frac{1}{100}$ - $\frac{1}{50}$ grain. No effect on the blood pressure was observed./

observed.

Camphor. Four series of observations were made on the effect of camphor in doses of .1 - .3 gram. No effect on the blood pressure was observed.

Cotarnine. Three series of observations were made on the effect of cotarnine hydrochloride in doses of $\frac{1}{2}$ - 1 grain. No effect on the blood pressure was observed.

Digitoxin. Three series of observations were made on the effect of large doses of two preparations said to consist of digitoxin, and two series on the effect of a preparation said to consist of a glucoside resembling digitoxin. No effect on the blood pressure was observed.

Ergotoxin. Four series of observations were made on the effect of ergotoxin quinate in doses of $\frac{1}{100}$ - $\frac{1}{50}$ grain. No effect on the blood pressure was observed.

Eserin. Three series of observations were made on the effect of eserin salicylate in doses of $\frac{1}{100}$ - $\frac{1}{50}$ grain. It elevated both the systolic and diastolic pressure, and caused nausea, vomiting and faintness. Its use as a blood pressure elevator was not considered advisable.

Pituitary Extract. Five series of observations were made on the effect of a 20% solution of pituitary extract in doses of $\frac{1}{2}$ - 2 cc. On one occasion it was

not/

not observed to have any effect, but on four occasions it lowered the systolic pressure. It was suggested that, for certain reasons, its effect in cases of marked hypotension might be different, but it was considered of very doubtful value.

Strychnine. Four series of observations were made on the effect of strychnine hydrochloride in doses of $\frac{1}{15}$ - $\frac{1}{10}$ grain. No effect on the blood pressure was observed.

Tyramine. Six series of observations were made on the effect of tyramine in doses of .04 - .08 gram. A powerful and rapid elevation of the systolic pressure was produced and lasted 10 - 15 minutes. The diastolic pressure was unaffected and practically no unpleasant symptoms were caused. Tyramine was considered a safe and effective blood pressure elevator.

REFERENCES.

Barger and Carr, Journal of Chem. Soc., XCI, p.337.

Blumfeld, Proceed. of Roy. Soc. Med., 1911, vol.IV, No.5, pp.28-30

Briggs and Cook, Johns Hopkins Hosp. Rep. 1903, vol.XI, pp.512, 515.

Cow, Proceed. Roy. Soc. Med., 1911, vol.IV, Pt.111, Pharmac. Sect. pp.81, 82, 84, 86-89.

Crile, Surgical Shock, 1899.

Cushny, Pharmacology and Therapeutics, 1910, pp.337,725.

Dale, Journ. of Physiol., vol.XXXIV, p.163, vol.XXXIX, p.25.

Depree, Brit. Med. Journ., vol.1, 1913, p.879.

Dixon, Practitioner, March, 1911, p.362.

Edgecombe, Practitioner, April, 1911, pp.531-536.

Faught, Blood Pressure, 1913, pp.50, 266.

Fortescue-Brickdale, Guide to the Newer Remedies 1910, pp.131, 135.

Gordon, Edin. Med. Journ., Jan., 1910, p.34.

Gibson, Edin. Med. Journ., March, 1911, pp.201-211.

Hale-White, Materia Medica, 1911, p.635.

Hirschfelder, Diseases of Heart and Aorta, 1913, pp. 251-252.

Lemann, American Journ. of Med. Scien., 1911, vol.II, p.865.

Malcolm, The Physiology of Death from Traumatic Fever, 1893.

McKenzie, Diseases of the Heart, 1913, pp.354, 377.

Price, Brit. Med. Journ., 1912, vol.II p.691.

Price, Clinical Journ., Aug., 28th, 1912, p.335.

Schäfer and Oliver, Journ. of Physiol., 1895, vol. XVIII, p.230.

Scott/

Scott, Practitioner, Aug., 1912, p.259.

Thorn, Practitioner, April, 1912, pp. 593-598.

Warfield, Interstate Med. Journ., vol.XIX, p.860.

Whitla, Materia Medica, 1910, p.605.

Williams, Latham and English's System of Treatment, vol. I, p.1285.

Williams, Clinical Journal, May 18th, 1910, p.93.

Some Observations on the Value of Drugs as Blood Pressure Elevators.

By Allan Watson M.D., D.P.H., Edin.
Lieutenant Royal Army Medical Corps

The investigations recorded here were made to determine what effect, if any, certain drugs, commonly supposed to act as blood pressure elevators have on the systolic and diastolic pressure of healthy individuals. The observations made were limited to the immediate effect of the drugs experimented with as one of the objects of the research was to endeavour to compare their values as possible remedies for combating dangerous hypotension.

Many drugs are said to have a pressor action simply because the cause a rise of blood pressure when administered experimentally to laboratory animals, but it does not necessarily follow that they will have a similar effect on human subjects. My observations were made on persons with normal arterial tension rather than on patients suffering from pathological hypotension, partly because of the difficulty or impossibility in such cases of insuring with reasonable certainty that the blood pressure of the patient remains unaffected by anything but the drug administered, but chiefly because the condition of the vessels in cases of marked

pplexion has not yet been definitely determined.

Most of the observations were made on the effect of drugs on the blood pressure of one male subject afterwards called the test subject. He was 26 years of age, in sound health, and had an average systolic and diastolic pressure of about the generally accepted normal. In a few instances the conclusions arrived at were confirmed by observations made on other healthy individuals.

The blood pressure readings were all taken by Korotkow's auscultatory method, the same mercurial sphygmomanometer being used in every case. The systolic pressure was read at the commencement of the first phase of the pulsation beat (the upper limit of the throb), and the diastolic pressure at the commencement of the third phase (the lower limit of the throb). All observations were made with the subjects in the sitting posture, the sphygmomanometer armlet being applied to the left upper arm at the heart level.

Before investigating the effect of any drugs on the test subject a considerable number of observations were made on his blood pressure to ascertain in what circumstances it could be maintained at the most approximately uniform level. His average systolic ~~pressure~~ pressure was found to be

about 125 mm. Hg.; the highest systolic pressure observed was 146 mm. Hg., and the lowest 110 mm. Hg. His average diastolic pressure was about 64 mm. Hg.; the highest diastolic pressure observed was 76 mm. Hg., and the lowest 42 mm. Hg. There was very little difference between the average forenoon, afternoon, and evening readings. The effect of various factors known to ~~have a transitory effe~~ influence the blood pressure transitorily were each investigated on several occasions; ~~In no case did these factors produce effects which differed particularly from those found by other observers, and on every occasion any effect produced had passed off in less than an hour and a half~~ in every case any effect produced was found to have passed off in less than an hour and a half. Several series of frequent observations on his blood pressure and pulse rate were then made, each series extending over a period of about three hours. For two hours before they commenced and while they were in progress he endeavoured to do nothing which would be likely to affect the blood pressure, and for about half an hour before they commenced and while they were in progress he remained seated in one room the temperature of which was kept approximately

uniform. It was found that the systolic and diastolic pressures as a rule varied very little if, at the commencement of a series of observations, they corresponded fairly closely to the average pressures already noted. On the other hand if they were abnormally high or low at the commencement of a series they generally fell or rose to about normal in the course of half an hour or so. The pulse rate on every occasion varied scarcely at all.

Most of the drugs used in these experiments are commonly etc - - - - . (continue here pages 7 and 8 of Thesis, omitting heading of page 7. Continue ~~[illegible]~~ section headed 'adrenalin' at end of water on page 8 of Thesis)

Adrenalin

(See next page of MS.)

Adrenalin

Some account was already been published in the PRACTITIONER * of observations made on another occasion on the effect of hypodermic injections of adrenalin on the test subject and two other healthy male subjects. The preparation used was the 1 in 1000 solution of adrenalin chloride made by Parke, Davis & Co., and 10 mins. of this solution were administered.

It was found to act very rapidly on both the systolic and diastolic pressure; a marked elevation of the former occurred and an even more marked depression of the latter. It also caused faintness, tremulousness, palpitation, and abnormally deep respirations. The suggestion was made that the effect of adrenalin might be due to its producing a temporary aortic regurgitation.

These observations and others made subsequently have led me to conclude that adrenalin is a dangerous drug which should always be used with caution and never as a general blood pressure elevator.

Eserin

Three series of observations were made on the effect of eserin on the blood pressure of the test subject. The preparation used was eserin salicylate U.S.P.: the effect of $\frac{1}{100}$ th grain was investigated on two occasions

* January 1914 pp. 94-99

and the effect of $\frac{1}{50}$ th grain on one occasion.

The first series of observations were made on the effect of $\frac{1}{100}$ th grain of eserin salicylate. The following table shows the effect of this dose on the blood pressure and pulse rate: —

Table I

(Here insert table on page 53 of thesis, omitting heading "Eserin Table I" and column headed "Pulse Pressure")

(Follow tabular matter on page 52 of thesis omitting last 2 lines — "Details — Table")

A second series of observations on the effect of $\frac{1}{100}$ th grain of eserin salicylate were made three days after those just recorded. The following table shows how the blood pressure was effected in this experiment: —

Table II

(Here insert table on page 55 of thesis omitting heading "Eserin Table II" and column headed "Pulsepressure")

(Follow table by matter on page 54 of thesis omitting last two lines — "The .... table")

The third series of observations was made on the effect of $\frac{1}{50}$ th grain of eserin salicylate. The effect of this dose on the blood pressure and pulse rate is shown by the following table: —

Table III

Table III

(Use mist table on page 58 of thesis omitting heading "Eserin Table III" and column headed "Pulse Pressure" Follow table by matter on page 56 of thesis after chart and on page 57 except last 2 lines — "The --- table" Omit also — "the faintness and nausea increased until I felt almost too ill to continue the observations" — page 57 lines 9 and 10)

Eserin was the only drug which I found to elevate both the systolic and diastolic pressure; a transitory elevation of the former and a rather more persistent elevation of the latter was produced. The pulse rate remained unaltered and the force of the cardiac contraction was never appreciably increased. It caused distressing nausea, vomiting, and faintness and for this reason its use in cases of hypotension would not seem to be advisable.

Pituitary Extract.

Two series of observations were made on the effect of pituitary extract. The preparation used was a sterilised 20 % solution. Four series of observations were made on the effect of the drug on the blood pressure of the test subject; one series on the effect of 0·5 cc. of this solution; one series on the effect of 2 cc.;

two separate series on the effect of 1 cc. One series of observations were also made on the effect of 1cc. on a female subject who had an abnormally low blood pressure

The following table shows the effect of 0.5 cc. on the blood pressure of the test subject: —

Table IV

(Here insert table on page 62 of thesis, omitting heading "Pituitary Table I" and column headed "Pulse Pressure" Follow table with matter on page 61 of thesis omitting last 2 lines — "The ---- table")

The effect of 1cc. of pituitary extract solution on the blood pressure of the test subject is shown by the following table: —

Table V

(Here insert table on page 64 of thesis omitting column headed "pulse pressure" and heading "Pituitary Table II")
(Follow table by matter on page 63 of thesis beginning with "Below chart" omitting last 2 lines)

A second series of observations were made on the effect of 1cc. of pituitary ~~extract~~ solution. The following table shows the effect on the blood pressure on this occasion: —

Table VI

Table VI

(Here insert table on page 66 of thesis omitting heading and column headed "pulse pressure." Follow table by matter below chart on page 65 of thesis omitting last 2 lines)

The effect of 2 cc. of pituitary extract solution on the blood pressure of the test subject was investigated on one occasion, and observations were made at frequent intervals for a period of four hours after the drug was administered. The following table shows the effect of this dose:—

Table VII

(Here insert table on page 68 of thesis omitting heading and column headed "pulse pressure" Follow ~~table~~ by matter below chart on page 67 of thesis omitting last 2 lines.)

(Follow above by matter and table on page 69 of thesis omitting column headed "pulse pressure" and heading the table — Table VIII instead of present heading

Table VIII

When administered to the test subject pituitary extract on each occasion caused a considerable fall of the systolic pressure while the diastolic pressure and pulse rate remained unaffected, and no unusual sensations were experienced even with the largest dose. In the case of the female subject the drug was not observed to have any appreciable effect.

According to Cow* pituitary extract dilates the splanchnic vessels although it constricts the systemic, and the constricting effect he found the drug to have on the systemic vessels generally did not appear to outweigh the dilating effect on the splanchnics. His experiments suggest a possible explanation of the rather surprising effect I found the drug to have on healthy individuals. It is possible that in cases of hypotension the splanchnic vessels are already more or less ..... (continue from here water on page 70 of thesis line 11 to end, and add in same paragraph —)

Unless this explanation is correct I can only conclude from my observations that pituitary extract, when administered to the human subject in medicinal doses, is of no value as a blood pressure elevator.

Tyramine

(See next page of MS)

* Proc. Roy. Soc. Med., 1911, Vol. IV. Pt. III Pharm. Sect. P.P. 86 – 89.

Tyramine

Tyramine (para-hydroxyphenylethylamine) is an organic base produced by the action of certain ferments on tyrosine. It is said to be the most important active constituent of watery extracts of ergot

Five series of observations were made on the effect of this drug on the blood pressure of the test subject One series was made on the effect of ·04 gram, two series were made on the effect of ·06 gram, and two series on the effect of ·08 gram. One series on the effect of ·06 gram was also made on another healthy male subject

The following table shows the effect of ·04 gram on the blood pressure and pulse rate of the test subject:-

Table IX

(Here insert table on page 79 of thesis omitting heading "Tyramine Table I" and column headed "pulse pressure". Following table insert matter below chart on page 78 of thesis omitting last 2 lines)

The following table shows the effect of ·06 gram of tyramine on the blood pressure and pulse rate of the test subject: —

Table X

(Here insert table on page 81 of thesis omitting heading Tyramine Table II and column headed "Pulse Pressure")
(Follow table by matter below chart on page 80 of thesis

omitting last 2 lines)

The following table shows the effect of another dose of .06 gram of tyramine on the blood pressure and pulse rate of the test subject :—

Table XI

(Here insert table on page 83 of thesis omitting heading Tyramine Table III and column headed "pulse pressure" Follow table by matter below chart on page 82 of thesis omitting last 2 lines)

The next table shows the effect of .08 gram of tyramine on the test subject :—

Table XII

(Here insert table on page 85 of thesis omitting heading and column headed "pulse pressure". Follow table by matter below chart on page 84 of thesis omitting last 2 lines)

The following table shows the effect of .08 gram of tyramine on the blood pressure and pulse rate of the test subject on another occasion :—

Table XIII

(Here insert table on p. 87 of thesis omitting heading and column headed "Pulse pressure". Follow table by matter below chart on page 86 of thesis omitting last 2 lines)

The following Table shows the effect of .06 gram of tyramine on the blood pressure and pulse rate of G. H., a healthy male subject, age 32.:-

Table XIV

(the next table on page 89 of thesis omitting heading and column headed "Pulse Pressure" Follow table by matter on page 88 of thesis below chart omitting last 2 lines)

~~In all my experiments tyramine was found to cause a marked elevation of the systolic pressure It did not appreciably affect the diastolic pressure and, except for slight transitory palpitation on two occasions, it caused no unpleasant symptoms~~

The effect of tyramine in all my experiments was to cause a considerable elevation of the systolic pressure; this effect was apparent in from 2 to 7 minutes and lasted for from 10 to 50 minutes. It did not appreciably affect the diastolic pressure and, except for slight transitory palpitation on two occasions, it caused no unpleasant symptoms. It seems to be an effective and safe blood pressure elevator, and I think that, injected hypodermically or intravenously, it should prove of great value in emergencies.

Series of observations, continued in each case for over an hour after the administration of the drug, were made on the effect of atropine, camphor, catarrine, digitoxin, ergotoxin, and strychnine on the blood pressure of the test subject. Only short notes of these observations are given as the results were in every case negative. My observations on the effect of these drugs have led me to the conclusion that they are of no value as blood pressure elevators when administered to the human subject in medicinal doses.

Atropine

Three series of observations were made on the effect of atropine sulphate, one series on the effect of $\frac{1}{100}$th grain and two series on the effect of $\frac{1}{50}$th grain. In no case was the systolic or diastolic pressure appreciably affected. The pulse rate appeared to be somewhat slowed by $\frac{1}{100}$th grain of atropine sulphate and accelerated by $\frac{1}{50}$th grain. Some dryness of the mouth was noticed on each occasion.

Camphor.

The effect of camphor was investigated on four occasions. The preparation used was a sterilised solution in olive oil. The effect of ·1 gram (1·5 grains) was investigated on one occasion, the effect of ·2 gram (3 grains) on two occasions,

the effect of .3 gram (4.5 grains) on one occasion. In no case was the drug observed to have any effect on the blood pressure or pulse rate.

Catarrine

Three series of observations were made on the effect of catarrine hydrochloride, two series were made on the effect of ½ grain and one series on the effect of 1 grain. In no case was any appreciable effect on the blood pressure or pulse rate observed, nor were any unusual sensations experienced.

Digitoxin

Digitoxin is said to be much the most active principle of digitalis and to act more powerfully on the vessels than some of the others. Five series of observations were made on the effect of this drug. Three different preparations, two said to contain a large proportion of the glucoside and one a considerable amount of it were used. ~~two~~ of $\frac{1}{50}$ grain. In no case was any appreciable effect detected.

Strychnine

Three series of observations were made on the effect of this drug on the test subject, the hydrochloride of strychnine being used. The effect of $\frac{1}{15}$ grain was investigated on one occasion, and the effect of $\frac{1}{10}$ grain on two occasions. In no case was

blood pressure appreciably affected, the pulse rate was slightly accelerated on one occasion after the administration of $\frac{1}{10}$ grain but was unaffected by the other doses investigated.

Conclusions

1. Atropine, camphor, cotarnine, digitoxin, ergotoxin and strychnine appear to be of no value as blood pressure elevators.

2. Adrenalin appears to be a dangerous drug which should always be used with caution and never as a general blood pressure elevator.

3. Eserin is an effective blood pressure elevator but on account of the distressing nausea, vomiting, and faintness it produces its use in cases of hypotension does not seem advisable.

4. Pituitary extract was found to have no pressor effect in my experiments. I have suggested that its effect in cases of marked hypotension may be different, but I consider it of doubtful value.

5. Tyramine appears to be a safe and effective blood pressure elevator.