THE TIME RELATIONS OF THE BLOOD-PRESSURE CHANGES AFTER EXCISION OF THE ADRENAL GLANDS, WITH SOME OBSERVATIONS ON BLOOD VOLUME CHANGES.

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THE experiments herein described consist of some controls made at the commencement of an investigation of the relation of the adrenals to vascular tone. It has long been known(1) that animals may survive the excision of both adrenal glands for one to three days or even longer, and that a low blood-pressure is found previous to the death of the animal, but the time at which such blood-pressure changes develop has not been so carefully investigated. Hoskins and McClure(2) have shown that no fall of blood-pressure is observed in half-an-hour after the removal of the adrenals, and Young and Lehmann(3) found no change of pressure for some hours. The evidence in this direction seems, therefore, to be mainly negative.

Method. Attempts have been made to measure the rate of the fall in blood-pressure in animals in which the adrenals were removed under ether anæsthesia (the animals being allowed to recover from the anæsthetic), in animals maintained the whole time under urethane anæsthesia, and also in animals previously decerebrated and therefore requiring no anæsthetic. It was also necessary to do controls to decide how long animals would maintain a normal blood-pressure under the same conditions if the adrenals were not excised. In the continuously anæsthetised and decerebrate animals a record of the blood-pressure was taken during the whole experiment, the carotid being connected to a membrane manometer (Porter's pattern) for this purpose.

A few control experiments on urethane anæsthesia were made on rabbits, but for all the other work cats were used. Frequent observations of the rectal temperatures were made, and the animals were kept as near normal as possible in this respect by the use of electric heating pads on the animal tables. No differences were detected as the result of differences of sex, nor did the time relations of the blood-pressure changes appear to be affected by section of both vagi, which was done in some

experiments. The sciatic nerve on one side was also divided and stimulated with faradic currents in many experiments; here it was noticed that the more frequent the stimulation the more rapid was the fall of blood-pressure, and the earlier the fatal result. The urethane was given in solution in water by a stomach tube, and was sometimes preceded by ether and at other times was itself used to induce anæsthesia. The question of dosage is discussed later. The excision of the adrenals was by the lumbar route, unless another method is directly specified in the text.

Animals not continuously anæsthetised. Only two animals, both young females, were examined under these conditions[1]. The animals were anæsthetised with ether, the adrenals were excised aseptically by the lumbar route, and the animals were allowed to recover from the anæsthetic. The next day they were again anæsthetised with ether, were given a dose of urethane by the stomach tube (about three-quarters of a normal dose), and then the carotid blood-pressure and the pressor response to sciatic stimulation were recorded as quickly as possible. Blood-pressures of 55 mm. of Hg were found 18½ and 23 hours respectively after the excision of the suprarenals; in animals of this size such pressures represent a drop of pressure of 30 or 40 p.c. in 18 to 24 hours, but this method does not allow accurate estimations to be made. Allowance has also to be made for the effect of age, since young animals are said to stand the operation better than older ones.

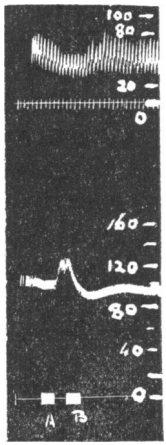

Fig. 1. Upper curve pressure of adrenalectomised animal, lower curve control animal for comparison. Time marker 5 sec. intervals. Signal marker stimulation of sciatic. *A*, control animal; *B*, adrenalectomised animal. (Exp. 2.)

Exp. 1. Cat. Female. Young. 1·7 kgm. Adrenals excised on 25. 6. 13—3.40 to 4.15 p.m.

26. 6. 13. 5.45 p.m. Cat well, eating steak. 9.30 p.m. Cat seemed weaker. 27th. 10.10 a.m. Animal very weak. Ether. Urethane 3 gm. 10.33 a.m. Record. Sciatic stimulation. Blood-pressure 55 mm. of Hg dropping to 40 mm. On sciatic stimulation rise of pressure of 20 mm. with marked respiratory variation in the blood-pressure.

Exp. 2. Cat. Female. Young. 1·5 kgm. Adrenals excised on 25. 6. 13—4.40 to 5.10 p.m.

26. 6. 13. 9.30 p.m. Animal contented and happy. 27th. 10 a.m. Cat quiet and rather weak. 3.45 p.m. Ether. Urethane 3 gm. 4.7 p.m. Record. Sciatic stimulation. Blood-pressure 55 mm. of Hg dropping to 40 mm. On sciatic stimulation rise of pressure of 15 mm. (40 to 55 mm.). Respiratory variations on the curve very marked. (See Fig. 1.)

[1] Both these experiments were performed in America in conjunction with Dr W. C. Quinby of Boston, Mass., U.S.A.

Urethane anæsthesia controls. Since in these experiments the blood-pressure was observed for 12 hours or more continuously, it was necessary to obtain controls of the effect of this anæsthetic on the circulation. The dose of anæsthetic was estimated on a surface area basis as proposed for toxins and drugs by Dreyer and Ray(4). The proper dose for animals of different size was arrived at in 1913 by Quinby and myself(5) by the application of these principles. We found Dreyer's formula to be the only one that allowed the dose to be calculated, so as to ensure a consistent depth of anæsthesia. In this way our results entirely confirmed Dreyer's principles, developed generally in a later paper by Dreyer and Walker(6). The exact dosage used is given in detail in the paper by Quinby and myself above referred to, and the full dose was near the minimal lethal dose for cats. In the absence, however, of any surgical procedure, such animals might recover. Thus, in the one experiment performed on this point[1], the cat, having received its dose of urethane by the stomach tube, slept for 48 hours without moving, yawned at 49 hours, fed at 52 hours and made a complete recovery. On the other hand with this dose of urethane no animal recovered from its anæsthetic, if it were also subjected to surgical procedures, demonstrating the additive effect of urethane and sensory stimulation. If urethane anæsthesia was accompanied by severe sensory stimulation, the time to death was more or less inversely proportional to the degree of stimulation and the amount of urethane given. Thus the longest survivals with the animals continuously on the operating table and with a continuous record of blood-pressure were obtained, when the vagi were not divided, the sciatics were not stimulated, and when only three-fifths of the normal dose of urethane was given, a little ether being given also from time to time as a supplementary anæsthetic when required.

In some experiments blood samples were also taken from the external jugular vein, were diluted with water (1 in 200), and were used for estimation of changes in blood volume by the comparison of the hæmoglobin values of the various samples in the Duboscq colorimeter. In cats a sample taken early in ether anæsthesia, before the giving of urethane was taken as the normal, but a few experiments were also performed on rabbits[2], blood samples being in these cases taken from the ear vein

[1] Experiment at Harvard Univ. Mass., U.S.A.

[2] Rabbits require about 10 p.c. more urethane than cats of the same weight, in order to produce a similar degree of anæsthesia. These animals were chosen owing to the ease with which blood samples can be taken from the ears.

TABLE I.* Controls of urethane anæsthesia in rabbits.

	Weight kgm.			First fall of B.P.	40 % fall of B.P.		Remarks
Exp. 3	3·4	0.00	Urethane 7·0 gm.	11.00 about	20.00 about	21.00 died	Stimulation of sciatic after 16.50. Rapid fall of B.P. 19.0.
Exp. 4	2·4	0.00	Ether	Continuous after urethane	—	4.40 killed	Overdose of urethane. 4.20. Adrenals removed.
		0.43	Urethane 7·0 gm.				
Exp. 5	2·4	0.00	Ether	Slight fall after urethane	—	6.40 killed	—
		0.50	Urethane 5·5 gm.				

TABLE II. Controls of urethane anæsthesia in cats.

Exp. 6	3·0	0.00	Urethane 6·0 gm.	No change in 6 hrs.	—	Killed	Sciatic stimulated. Adrenals excised at 6.20. Damage to splanchnics. Death 8.55.
Exp. 7	2·1	0.00	Urethane 4·75 gm.	No change in 4 hrs	—	—	Sciatic stimulated. Excision of adrenals at 4.0.
Exp. 8	2·1	0.00	Urethane 4·75 gm.	3.30	7.45	13.55	Sciatic stimulated.
Exp. 9	1·4	0.00	Urethane 3·75 gm.	8·30	20.30	21.00	—
Exp. 10	3·6	0.00	Urethane 6·5 gm.	7.40	21.10	24.50	High initial pressure.
Exp. 11	3·1	0.00	Ether	Fall on giving urethane. Further fall 5.30	—	25.25 killed. At this time only 23 % fall of B.P.	Sciatic stimulated for periods of 5 secs. on five occasions only. Three-fifths normal initial dose of urethane. Ether given during sciatic stimulation. Early pregnancy.
		0.30	Urethane 4·5 gm.				
		2.30	,, 0·7 gm.				
		5.30	,, 0·7 gm.				
		10.30	,, 0·7 gm.				
		22.12	,, 0·7 gm.				
Exp. 12	1·3	0.00	Ether	Fall on giving urethane. Further fall 11.0	17.30	22.20 killed	Three-fifths normal initial dose of urethane. Ether given when necessary.
		0·40	Urethane 2·5 gm.				
		11.45	,, 0·6 ,,				

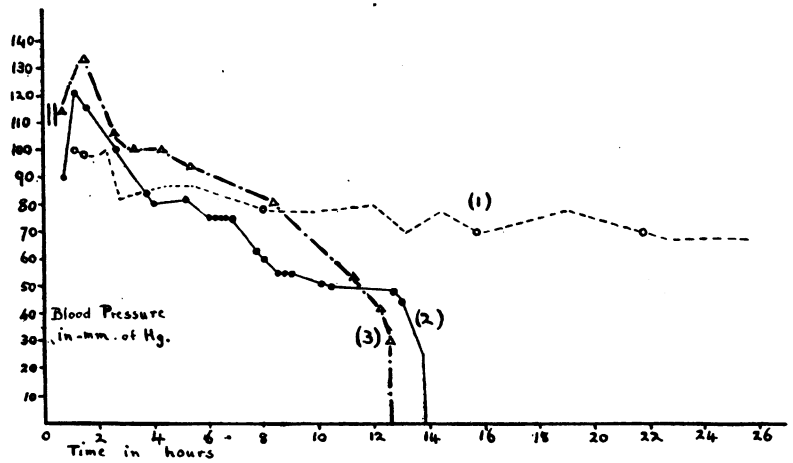

Fig. 2. Contrast between the blood-pressure changes seen with light urethane anæsthesia, deep urethane anæsthesia with sciatic stimulation, and deep urethane anæsthesia with adrenal excision.

(1) Light urethane anæsthesia (Exp. 11). ○. Sciatic stimulation for 5 secs.

(2) Deep urethane anæsthesia (Exp. 8). ●. Sciatic stimulation for 15 secs.

(3) Deep urethane anæsthesia and adrenal excision (Exp. 14). △. Sciatic stimulation for 15 secs. ||. Adrenal excision.

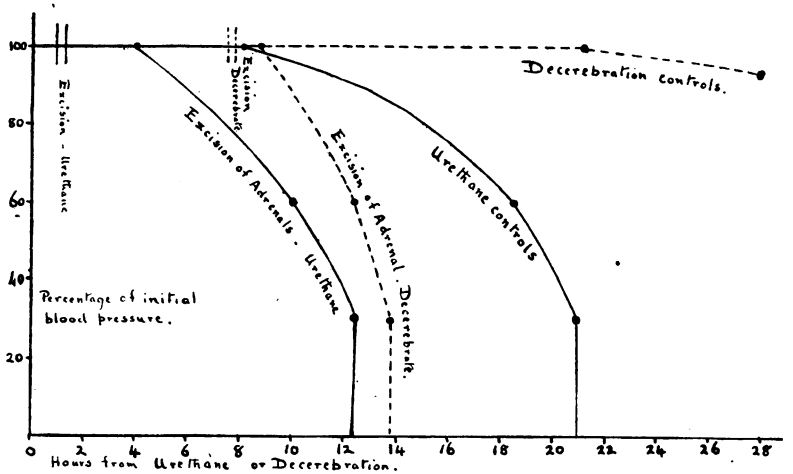

Fig 3. Contrast between time relations of blood-pressure changes in *average* results with urethane and decerebration and adrenal excision.

before and from the internal jugular after anæsthetisation. For the method I am indebted to Professor Dreyer.

The various controls for urethane anæsthesia are given in Tables I and II, and Figs. 2 and 3 show the same points diagrammatically. It was found that with urethane anæsthesia cats may survive from 14 to 25 hours or longer; that there is an initial fall of pressure of 10 to 20 p.c. when urethane anæsthesia supervenes on that due to ether, but that there is no further fall for from $3\frac{1}{2}$ to 11 hours. There is often some concentration of the blood when urethane is used according to this method, such concentration occurring especially in the early stages of anæsthesia, varying from nil up to 18 p.c., and usually being about 4 to 7 p.c. This blood concentration may be due perhaps to the osmotic action of a concentrated solution of urethane in the stomach, fluid being absorbed from the blood.

With the above figures for urethane anæsthesia may be contrasted the results obtained in Exp. 13 on a castrated male cat of 3 kgm. This animal proved to have a liver tumour, probably a carcinoma, though no histological examination was made. The experiment shows a very accelerated deterioration of the circulatory system in a diseased animal subjected to urethane anæsthesia and nerve stimulation. This contrast with the normal animal is comparable to that seen in man, when the production of "surgical shock" in the septic or carcinomatous patient is compared with that produced in a healthy man. This would suggest that the gradual deterioration seen under urethane anæsthesia and nerve stimulation is a change of a similar nature to that of "surgical shock" in man.

The details of this experiment are as follows (see Fig. 4):—

23. 12. 13. Cat. 3·0 gm. Urethane 6 gm. at 0.00, preceded by a little ether. Vagi cut. Sciatic stimulation at intervals for periods of 15 seconds.

0.45. B.P. 118. On stimulating sciatic rise of B.P. to 160 this rise being well maintained. Rectal temperature 32·5° C. Cheyne-Stokes respiration induced. 1.15. B.P. 105 with sciatic response to 127. A very slight secondary rise after stimulation also seen. Respiratory movements were regular. Rectal temperature 33° C. 1.25. Blood sample—taken as 100 p.c. 2.25. B.P. 85. Sciatic response to 105. Rectal temp. 34·5° C. 3.15. B.P. 77. Sciatic response to 90 mm. this rise being followed by a definite depressor reaction. Rectal temperature 36° C. The respirations resume a normal rate very soon after the cessation of the stimulus (see Fig. 4). 4.40. B.P. 57. Sciatic response to 67 mm. with marked later depressor reaction. Rectal temperature 37° C. 4.55. Blood sample 2=97 p.c. Hb. 5.45. B.P. 33. Sciatic response extremely small. Rectal temperature 36·5° C. 6.20. B.P. 35. Blood sample 101·5 p.c. Hb. Rectal temperature 36·5° C. 7.5. Respiration ceased. Death.

The experiment is of interest since it illustrates the changes seen

with urethane anæsthesia and nerve stimulation in any animal, the only difference to be detected between the record and one obtained under similar circumstances in a normal cat being the far greater rapidity with which the changes developed. Difficulty was experienced in maintaining the body temperature constant in this animal, and this may have contributed to its rapid failure, but it is clear that any such results, where a definite pathological condition can be recognised, should not be included in the general averages.

Adrenal excision in urethaned cats. The results obtained on excision

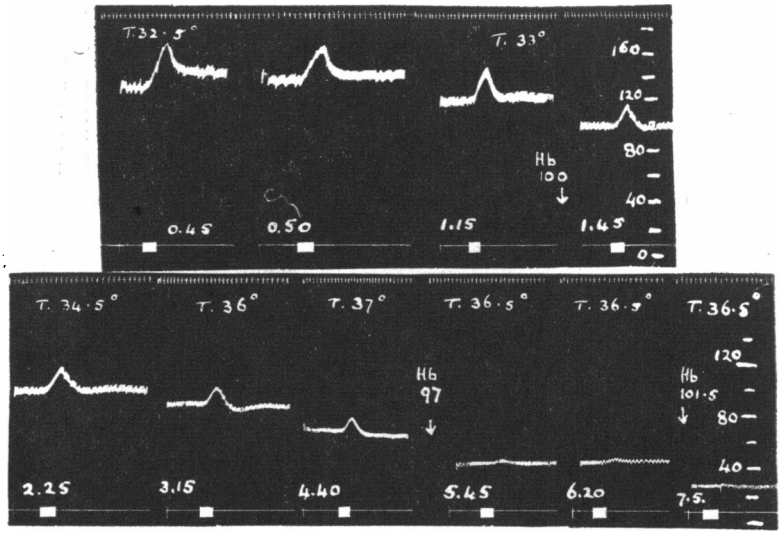

Fig. 4. Urethane anæsthesia with sciatic stimulation in diseased cat (Exp. 13). Record shows the change in the pressor response, with a change in the respiratory response (as seen by the respiratory variations in blood-pressure). Time marker 5 sec. intervals.

of the adrenals in cats under similar conditions of urethane anæsthesia may be seen in Table III, and the average results are contrasted with those of the control animals in Fig. 3. It will be noticed that if the anæsthesia is light and stimulation is as far as possible avoided, the animals with adrenals excised die considerably quicker than the control animals. Roughly the time taken in going down hill is reduced to about 67 p.c. of the normal value. On the other hand it is remarkable that if the control animals are subjected to deep anæsthesia and constant nerve stimulation, there is very little difference between the times to

TABLE III. Urethane anæsthesia and adrenal excision in cats.

	Weight kgm.			Time excision of adrenals	First fall of B.P.	40 % fall of B.P.	Death from beginning anæsth.	Death from excision of adrenals	Remarks
Exp. 14	3·0	0.00	Ether Urethane 6·0 gm.	0.45	2.15	9.45	12.45	12.0	Sciatic stimulated. Excision by abdomen (Fig. 5).
Exp. 15	3·5	0.00	Ether Urethane 6·5 gm.	2.0	3.0	—	3.0	—	Killed. Sciatic stimulated.
Exp. 16	2·1	0.00	Ether Urethane 4·75 gm.	4.0	9.0	13.00	14.30	10.00	Sciatic stimulated. Adrenalin injected at 3.01 and at intervals later—in all. 3 mgm.
Exp. 17	3·3	0.00	Urethane 6·25 gm.	1.45	6.15	7.35	10.55	9.10	Very sudden fall of B.P.
Exp. 18	2·5	0.00	Urethane 5·0 gm.	2.0	2.45	—	4.20	2.20	Died probably from asphyxia. Mucus in trachea.
Exp. 19	2·1	0.00	Ether Urethane 2·6 gm.	1.30	6.00	—	Killed	—	Light urethane anæsthesia—ether as required. Sciatic stimulated occasionally.

death of the adrenal-free and control animals. (Compare for instance the results obtained in Exps. 14 and 16 in Table III with those of Exp. 8 in Table II.) (See also Fig. 2.)

On contrasting the time relations of the blood-pressure changes in these adrenal-free animals under urethane with those obtained in etherised animals allowed to recover from their anæsthetic, it is clear that the fall of blood-pressure is much accelerated in the animals subjected to prolonged urethane anæsthesia. Thus in the urethane animals the first fall of blood-pressure occurs usually about three hours after the excision of the adrenals and a 40 p.c. fall of blood-pressure is seen after about eight hours. On the other hand the etherised animals only showed a 30 to 40 p.c. fall in 18 to 24 hours, although they too were eventually exposed to urethane anæsthesia.

The splanchnic nerves are easily injured in attempting to remove

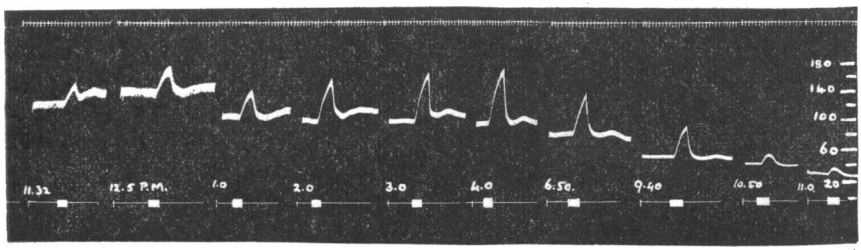

Fig. 5. Fall of pressure on excision of adrenals under urethane (Exp. 14). Time marker 5 sec. intervals.

the adrenals, but any such injury is readily recognised, since it causes an immediate fall in blood-pressure with the partial or complete disappearance of the normal pressor response to sciatic stimulation. This pressor response was never decreased immediately as the result of excision of the adrenals, nor was there as a rule any immediate and maintained fall in blood-pressure, unless the splanchnic nerves had been injured.

An example of the blood-pressure changes observed after excision of the adrenals under urethane is given in Fig. 5 and this record also demonstrates the changes seen in the pressor response to sciatic stimulation. The record commences immediately after the excision of the adrenals and represents the experiment numbered 14 in Table III. Besides the changes in the blood-pressure tabulated in Table III the record illustrates also how the pressor response to sciatic stimulation undergoes no diminution for a considerable time ($4\frac{1}{2}$ hours), and that

in fact during this early period the sciatic response often increases slightly if the maximum pressure attained be noted, usually increases considerably if the absolute rise on stimulation be taken as a guide, and always increases enormously if the percentile rise be used as a measure. While it is conceivable that the animal reacts to its condition by an increased activity of the vasomotor centres, yet it seems more probable that the reaction remains little altered, and that the maximum pressure attained gives the more accurate measure. The slight rise in this value might then readily be explained by the increased blood volume which is demonstrated under these conditions by the method of estimating the hæmoglobin percentage. The results in this experiment may be given in a table.

Time after excision of adrenals	Maximum pressure on sciatic stimulation	Absolute rise on sciatic stimulation	Percentile rise on sciatic stimulation
0·07	144 mm.	29 mm.	25·2 %
0·40	163	30	22·5
1·35	135	30	28·6
2·35	150	50	50·0
3·35	158	58	58·0
4·35	163	70	75·3
7·25	130	50	62·5
10·15	90	37	69·8
11·25	53	11	26·2
11·25	37	7	23·3

Thus it is seen that the maximum value attained remains remarkably constant on the whole during the first four hours and this can hardly be a coincidence. On the other hand the percentile method of comparison would indicate that the last response recorded—just before death—was of equal intensity with that recorded just previous to adrenal excision, which seems improbable. The results would seem to be much more in accordance with the theory that, while the vascular tone decreased, the response to sciatic stimulation remained unchanged; these results do not therefore support the use of the percentile measure of blood-pressure changes as suggested by Porter(7) in the same animal at any rate under these conditions; on the other hand there can be little doubt that Porter's is the best method for comparison of different animals. There appears to be no noticeable diminution in the sciatic response until the mean pressure has fallen below about 60 mm. and this diminution may therefore be secondary to the low blood-pressure. In other cases the height reached on sciatic stimulation fell steadily after adrenal excision, the fall being more or less parallel to the fall of blood-pressure, so that a maintained sciatic response does not appear to be invariably seen after

adrenal excision. There is therefore no constant difference to be detected between the changes noted after adrenal excision and the progressive deterioration seen with prolonged urethane anæsthesia. In fact the changes observed after adrenal excision often resembled those seen in Fig. 4.

Decerebrate animals. Controls. Some excisions of the adrenals were performed on decerebrate cats. Here again it was necessary first of all to do controls to discover the normal "life" of a decerebrate preparation. Table IV gives the control experiments. It will be seen that the maintenance of blood-pressure is relatively infinite, even in the ordinary "dirty" preparation. If decerebration be performed aseptically and the cranial cavity is filled with paraffin wax, death may be postponed for days or weeks (8). Many animals may be lost owing to recognizable complications such as hæmorrhage or asphyxia; these animals are not included in the general averages. It is absolutely essential that the body temperature should be controlled artificially and maintained at a normal level. The collection of mucus in the trachea depends on a number of factors among the most important being the use of ether as an anæsthetic (chloroform being more satisfactory), ligature of the carotids causing anæmia of the respiratory tract, fixation of the head preventing effective coughing, and tracheitis following the introduction of a cannula. In these experiments the decerebrations were performed by trephining according to Sherrington's older method (9), and I am indebted to Professor Sherrington for personal instruction in this method. The carotids were tied either permanently or temporarily, and the above complications were avoided as far as possible. When blood volume changes were being observed, ether was used as the anæsthetic until the first blood sample had been taken, since Dreyer and Walker (10) have shown that ether anæsthesia does not cause any alteration of the hæmoglobin percentage.

Adrenal excision in decerebrate cats. Table V gives the results obtained on excision of the adrenals in these animals, and Fig. 3 shows the average results and compares them with those in control animals.

It will be seen that, in marked contrast to the stability of the control preparations, the blood-pressure falls quickly after excision of the adrenals, much earlier than with anæsthetised animals. Thus the first fall of blood-pressure occurs within about $1\frac{1}{4}$ hours and death in $6\frac{1}{4}$ hours, as compared with $2\frac{3}{4}$ hours and $10\frac{1}{2}$ hours with urethane anæsthesia. It will also be seen that a slight increase in the blood volume on excision of the adrenals occurs under these conditions, as with urethane anæsthesia.

TABLE IV. Decerebrate cats. Controls.

	Weight kgm.	Preliminary anæsthesia	Decerebrate	First fall of B.P.	40 % fall of B.P.	Remarks
Exp. 20	4·3	Ether	0.20	18.00 about	—	Rectal saline. Died from asphyxia. Mucus in trachea.
Exp. 21	3·9	Ether. C.E.	0.40	24.00 about	49.00 about	Killed 50.00. Saline by rectum. Milk by stomach at intervals.
Exp. 22	2·4	C.E.	0.30	No fall in 9 hrs	—	Killed.

TABLE V. Decerebrate cats. Adrenal excision.

	Weight kgm.	Preliminary anæsthesia	Decere-brate	Adrenals excised	First fall of B.P.	40 % fall of B.P.	Death from beginning anæsthesia	Death from excision of adrenals	Remarks
Exp. 23	3·0	Ether	1.10	2.10	2.50	—	5.30	3.20	Mucus in trachea death probably from asphyxia.
Exp. 24	2·9	Ether. C.E.	0.40	4.50	4.50	10.00	10.30	5.40	—
Exp. 25	4·0	C.E.	0.40	6.30	11.00	16.30	18.30	12.00	Adrenalin injected 17.40.
Exp. 26	3·4	C.E.	0.40	13.00	13.15	16.05	17.20	4.20	Mucus in trachea.
Exp. 27	2·7	C.E.	0.40	4.50	5.30	6.30	9.30	4.40	Sciatic stimulated Fig. 6.
Exp. 28	1·8	C.E.	1.25	3.30	4.0	—	5.0 killed	—	B.P. fallen 110 to 85, *i.e.* 23 % in last hour.

Fig. 6 illustrates the effect of excising the adrenals in a decerebrate preparation, a case in which the quickest fall of blood-pressure yet observed was obtained (Table V, Exp. 27). The record shows a slight immediate fall of pressure on excision of the adrenals, though after this the pressure rose again slightly for 40 minutes, when a gradual fall of pressure set in leading to death 4.40 hours after the excision of the adrenals. That the splanchnic nerves were not injured during the operation was evident from the fact that the sciatic response (only occasionally induced) was at first in no way impaired.

Blood volume changes. Recently changes in the blood volume have attracted much attention. At the time these experiments were performed (1914) the blood volume changes were estimated in order to control the

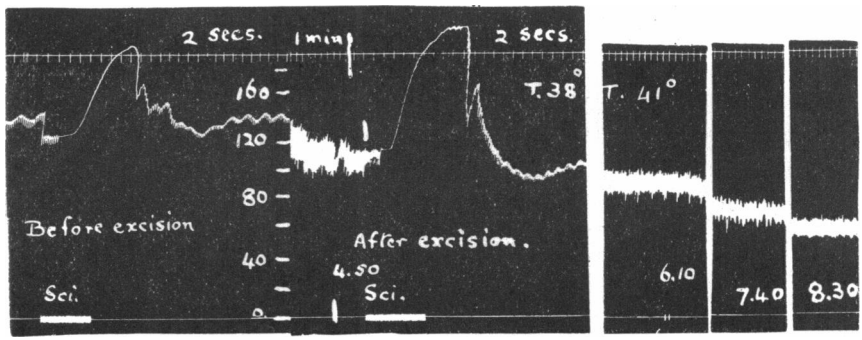

Fig. 6. Excision of adrenals in decerebrate cat (Exp. 27). Signal-stimulation of sciatic. Time marker 2 secs. and 1 minute. Up strokes on 2nd part of curve indicate corresponding points on record.

other results obtained[1]. For convenience all the observations made in this research on blood volume changes are collected together in Table VI, but unfortunately they are somewhat incomplete, having been made only in a small percentage of the experiments. The marked contrast between the effects of a fall of blood-pressure due to hæmorrhage on the hæmoglobin percentage and those of a similar fall due either to prolonged urethane anæsthesia or to excision of the adrenals is none the less very noticeable. In the first case the hæmoglobin is rapidly diluted and an effort seems to be made to keep the blood volume constant, while in the second case there is only slight absorption of fluid

[1] My thanks are due to Prof. Dreyer, who was entirely responsible for any attention I have paid to these changes. He first pointed out to me the importance of this subject, and I adopted his method of estimation.

in spite of the great fall in blood-pressure. In none of the cases investigated, where the blood-pressure fell as the result of anæsthesia, "shock," or adrenal excision, did the dilution of the hæmoglobin amount to a change of more than 6·5 p.c., and only once did it exceed 5 p.c.; on the other hand in Exps. 22 and 25 where considerable hæmorrhage occurred a dilution of blood amounting to 25 p.c. or over was observed.

Some interest is attached to Exp. 33 included in this table, where a dilution of the blood of 10 p.c. is seen. In this case there was no hæmorrhage but some injury to the splanchnic nerves had probably occurred. It therefore provides some slender evidence that injury to the splanchnic nerves with a consequent fall in blood-pressure may have more effect in causing dilution of the blood than adrenal excision. Unfortunately the only other experiment in which the splanchnic nerves were injured and blood samples were also taken (Exp. 35, Table VI) was complicated by the recurrence of hæmorrhage from the brain at the time.

Discussion of results. Most of the results here described are chiefly important as a basis for further work, the experiments having been planned as controls. Certain of them, however, have some interest as they stand and may be considered shortly here.

The experiments have demonstrated that not only is there no immediate fall of blood-pressure on excising the adrenals, but also that this fall of blood-pressure may be considerably delayed. This is of no great theoretical importance since additional chromaffine tissue exists in the cat along the aorta (11), so that in these experiments there has been no complete excision of chromaffine tissue. On the other hand it is remarkable that the blood-pressure changes progress much more quickly in the decerebrate animal than in the animal under urethane anæsthesia, while they progress quicker too in these anæsthetised animals than in others allowed to recover from their anæsthetic. These results are rather difficult to explain. The quicker development in the anæsthetised animal probably depends on the exhaustion of the chromaffine cells, since Elliott (12) has demonstrated the marked effect of urethane and also of sensory stimulation in producing an exhaustion of the suprarenals. If this is true, then a similar explanation may be brought forward to account for the fact that sensory stimulation greatly shortens the life of an animal under urethane anæsthesia, since death under these circumstances may be due to an exhaustion of the adrenal glands in an animal unable to replace its losses while anæsthetised. Attention has already been drawn to the similarity existing in the curves obtained for the

TABLE VI. Observations on hæmoglobin changes. Experiments up to 28 have been referred to in the text or in the Tables I–V.

	Weight kgm.		Time	B.P.	Hb percentage	Remarks
		A. Rabbits.				
Exp. 4	2·4	0.00 Ether	0.20	90	100	Variations of rectal temp. from 35° C.
		0.43 Urethane 7·0 gm.	0.57	66	100·4	to 38·25° C.
			1.27	53	100	
			2.30	49	98·3	
			3.50	41	99·7	
Exp. 5	2·4	0.00 Ether	Before ether	—	100	
		0.50 Urethane 5·5 gm.	0.40	80	112	
			1.5	87	100	
			1.25	85	100	
			2.50	60	95·6	
			4.15	80	98	
			6.40	—	106·3	
Exp. 29	2·3	Ether	0.20	84	100	Vagi cut 0.30.
			2.30	80	107	
Exp. 30	3·1	0.00 Urethane 7·0 gm.	Before urethane	—	100	No incision. Death at 9.30. Mucus in
		3.45 „ 2·0 „	1.45	—	118·7	trachea.
			4.45	—	118·7	
Exp. 31	2·2	0.00 Urethane 5·5 gm.	Before urethane	—	100	No incision. Animal fell when anæs-
			0.40	—	100·3	thetised and broke femur.
			2.00	—	100·2	
			4.30	—	106·3	
		B. Cats.				
Exp. 7	3·0	0.00 Ether	1.25	105	100	Cf. Fig. 4.
		Urethane 6·0 gm.	4.55	57	97·5	
			6.20	35	101·5	
Exp. 11	3·1	0.00 Ether	0.30	135	100	4.50 rectal saline 15 c.c. 17.30 rectal
		0.30 Urethane 4·5 gm.	2.20	90	106·5	saline 10 c.c. Early pregnancy.
		and at intervals later in	9.57	75	104·1	
		all 7·3 gm. and a little	21.12	75	103	
		ether as required				

Exp. 32	2·7	0.00 Ether	0.35	—	100	Slight continuous fall of B.P. after urethane, and very slight fall on excision of adrenals.
		0.40 Urethane 3·3 gm.	1.20	—	114	
		3.45 „ 0·5 „	4.45	—	110	
		4.35 „ 0·7 „	5.25	—	107·5	
		5.20 Adrenals excised				
Exp. 21	3·9	0.00 Ether. C.E.	0.20	—	100	3.30 to 29.25 five injections of rectal saline 30 to 50 c.c. each. 25.35 80 c.c. milk by stomach tube. 35.40 90 c.c. milk by stomach tube. Ether alone till first blood sample taken.
		0.40 Decerebrate	1.48	140	97·8	
		26.00 Sciatic cut and stimulated	7.35	160	99·2	
			13.25	160	93·5	
			19.15	160	100	
			25.45	120	100·8	
Exp. 24	2·9	0.00 Ether. C.E.	0.15	—	100	Ether alone till first blood sample taken.
		0.40 Decerebrate	2.0	—	97·5	
Exp. 18	2·5	0.00 Urethane 5·0 gm.	1.40	87	100	Mucus in trachea.
		2.00 Adrenals excised	4.0	50	96·7	
Exp. 25	4·0	0.00 C.E.	0.15	—	100*	* Percentage perhaps not normal owing to action of chloroform.
		0.40 Decerebrate	5.40	110	110	
		6.30 Adrenals excised	7.5	95	105	
			10.30	97	111	
			17.0	50	104	
Exp. 33	2·0	0.00 C.E.	2.15	90	100	3.15 some blocking of trachea. 8.20 to 11.45 150 c.c. of milk and water by stomach tube. 12.15 artificial resp. required. 12.30 dead.
		0.40 Decerebrate	5.30	78	100	
		7.30 Adrenals excised	7.50	62	90	
		B.P. fall 78 to 62	11.30	50	92	
		? injury to splanchnics	12.20	20	91	
Exp. 34	4·1	0.00 Ether. C.E.	0.15	—	100	Much hæmorrhage during decerebration. Ether only till first blood sample taken.
		0.40 Decerebrate	3.25	92	75·6	
			4.20	70	75·4	
Exp. 35	2·2	0.00 C.E.	0.20	—	100†	† Percentage perhaps not normal owing to action of chloroform.
		0.35 Decerebrate	5.22	105	85·3	
		5.30 Adrenal veins clamped	6.18	55	83	Much hæmorrhage from skull during decerebration and at 5.30.
			7.15	38	73·5	

blood-pressure changes in animals exposed to constant nerve stimulation under urethane, and in animals under the same conditions with the adrenals excised. The excision of the adrenals appears to make no difference. This can be seen again very clearly in Fig. 2 where the blood-pressure changes seen in three experiments with light urethane anæsthesia, deep urethane anæsthesia, and adrenal excision under urethane are all charted together.

The similarity between the curves for adrenal excision under urethane and simple urethane anæsthesia with stimulation might of course be explained by supposing that under urethane anæsthesia the animals died before any of the effects of the excision of the adrenals had time to develop. But this is not borne out by the other experiments. For it is found that cats with full urethane anæsthesia if not exposed to nerve stimulation will long outlast those with similar anæsthesia and excision of the adrenals, and it appeared from one experiment that even with very light urethane anæsthesia the onset of the first blood-pressure changes developed about the same time after the adrenal excision. It seems therefore more reasonable to explain the effects of urethane anæsthesia as due partly to its action on chromaffine cells. Definite conclusions are not warranted but one cannot help wondering whether deep urethane anæsthesia with constant sciatic stimulation does not in itself produce a physiological—or pathological—exhaustion of adrenal activity.

The contrast between the changes seen in the decerebrate preparation and the animals under urethane is illustrated by Fig. 3 and the difference is very great. The fall of blood-pressure not only develops earlier in the decerebrate preparation but it also progresses much more quickly. Many explanations are possible. There may occur an exhaustion of the additional chromaffine tissue as the result of the stimulus of the decerebration operation, but if this is so, it is remarkable that the control animals maintain their pressure so well. Or again it may be due to the blood-pressure in the decerebrate animal being abnormally high so that the mechanism for the maintenance of blood-pressure is severely tried and is unable to stand the additional injury of the removal of the adrenal glands. But the observed blood-pressures do not bear out this theory. Though high blood-pressures were often observed in the decerebrate animals, yet the average initial mean pressure observed in the decerebrate animal was 103 mm. as against an average initial blood-pressure in urethane animals of 90 mm. The blood-pressure in the decerebrate animals was therefore only 10–15 p.c. above that of the

urethane animals, and this in spite of the fact that the average weight of the cats was 3055 gm. in the decerebrate and only 2386 gm. in the urethane animals[1]. The blood-pressures observed therefore corresponded closely with those seen with ether anæsthesia. This explanation is therefore improbable. Other possible reasons are the division of the stalk of the pituitary gland during decerebration, or to an "addition" effect, due to the fact that the adrenal excision follows shortly after the animal has suffered from hæmorrhage during decerebration.

More recently some attempt has been made to test these theories, the adrenals having been excised in two cats, one decerebrated according to Sherrington's (13) later method, and consequently suffering little if at all from hæmorrhage though having the pituitary completely removed, and the second decerebrated aseptically according to my method (8) and used for adrenal excision about 28 hours later. In both these animals the fall of pressure was even more rapid than in the other decerebrated cats. The cat obtained by the use of the decerebrator died in about 2 hours after the adrenal excision, and the other done aseptically and kept for 28 hours only survived the excision for 2½ hours, though it was a healthy young cat. I hope to undertake further work on this point.

The effects of adrenal excision may be due to the gradual paralysis of the sympathetic nerve endings in the absence of adrenalin, but the experiments are not definite on this point. Some experiments (*e.g.* Exp. 4, Table III) even appear to suggest that this is not true, since the blood-pressure commences to fall while the pressor response to stimulation is well maintained or increased; but it may be argued that in this case the earlier part of the fall in blood-pressure is due to the anæsthetic rather than to the excision of the adrenals. Whether this type of change could be produced in decerebrate animals was not determined; in the earlier experiments repeated sciatic stimulation produced sooner or later reactionary hæmorrhage from the meningeal vessels, and therefore sciatic stimulation had to be avoided. In the later experiments, when the decerebrate animal was kept much longer, and when the cranium was often plugged with wax, reactionary hæmorrhage did not occur, but no determination of this point was made.

Lastly a few observations on blood volume changes are here collected together. The most noticeable feature is the maintenance of a fairly normal hæmoglobin percentage when the blood-pressure falls as the result of prolonged anæsthesia or the excision of the adrenals, while

[1] Higher blood-pressures were observed as a rule in older and larger animals than in the smaller and younger.

marked dilution of the blood occurs if the blood-pressure falls as the result of hæmorrhage. The results obtained also show that there may be a concentration of the blood during urethane anæsthesia, and though the figures obtained demonstrate that this is usually slight and transient, yet it might perhaps assume importance under certain circumstances, as for instance in experiments on sugar tolerance. No conditions of marked blood concentration were observed except in an animal suffering from asphyxia.

Conclusions.

1. On excision of the adrenal glands in cats no immediate fall in blood-pressure is seen, but the blood-pressure changes develop earlier and progress more quickly in the decerebrate animal than in one anæsthetised with urethane. Also these blood-pressure changes seem to develop more quickly under both these conditions than in animals anæsthetised with ether and allowed to recover from their anæsthetic.

2. Urethane anæsthesia may be used in cats for experiments lasting for 25 hours or longer. The blood-pressure observed is 10 to 20 p.c. lower than that seen in etherised or decerebrate animals and it commences to fall further after about eight hours anæsthesia or even earlier. Nerve stimulation accelerates this fall of blood-pressure.

3. Decerebrate preparations may be used for blood-pressure experiments lasting over several days if the body temperature is maintained normal, and if the animal is carefully "nursed." If aseptic precautions are taken they may be used over even longer periods.

4. If the adrenals are excised in the urethaned cat, the blood-pressure commences to fall 2 or 3 hours after the operation, and the animal dies in about $10\frac{1}{2}$ hours. The increase in the rapidity of the blood-pressure changes as compared with the control urethane animals is one of about 33 p.c.

5. Excision of the adrenals in the decerebrate animal leads to death in about six hours, the pressure commencing to fall about one hour after excision.

6. If the adrenals are excised under ether anæsthesia and the animals are allowed to recover from the anæsthetic, the fall in blood-pressure appears to be much slower. A fall of 30 to 40 p.c. only in 18 to 24 hours was found.

7. Some observations on blood volume changes have been made. With a fall in blood-pressure due to prolonged urethane anæsthesia little or no dilution of the blood takes place, and there may even be a slight

concentration. With excision of the adrenals an immediate slight dilution of the blood occurs, and the blood volume is perhaps increased since the operation is practically bloodless. Later when the blood-pressure falls there is little further dilution of the blood. If on the other hand the blood-pressure falls as the result of hæmorrhage, a rapid and considerable dilution of the blood is seen.

8. After excision of the adrenals the sciatic response to stimulation is at first slightly increased. At a later stage it may be well maintained, while the blood-pressure is falling, or the height reached on sciatic stimulation may fall in a manner more or less parallel to the changes in the blood-pressure level. With adrenal excision under urethane anæsthesia neither type of change was obtained constantly.

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