THE CONTROL OF THE SUPRARENAL GLANDS BY THE SPLANCHNIC NERVES[1]. By T. R. ELLIOTT, M.D.

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THERE is no clear knowledge[2] at present with regard to the share taken by the suprarenal glands in resisting various processes that are harmful to the body. For the last two years I have tried to gain some light on this question by analysing the state of exhaustion to which the human suprarenals are reduced in the different conditions leading to death in Hospital cases. Attention was paid chiefly to the loss of the normal load of cortical "lipoid" substance and of the adrenalin in the medulla, the gross total of the latter being measured quantitatively by physiological assay.

Unfortunately the conditions of fatal disease in man were found to be too complex to permit of simple analysis. Broadly summarising the results, it appeared that the glands suffered rapid exhaustion in cases of any microbic fever, of repeated simple hæmorrhage, and of surgical shock: but to distinguish clearly the value and nature of each of these factors was impossible. I therefore tried to reproduce each separately on experimental animals, in which the relationship of the nervous system to the glands could at the same time be studied.

Method. Cats were used in all the experiments. The lipoid in the cortex of the cat[3] is never so abundant as in the human gland: changes in its distribution were observed histologically, but they did not seem to follow any special cause, and they will be referred to only incidentally in this paper. It was therefore to the adrenalin content of the medulla that attention was in the main directed.

[1] A preliminary account of the results has been given in *Proc. Physiol. Soc.* This *Journ.* XLIII. p. xxvii. 1912.

[2] Reference is made here only to papers which bear directly on points under discussion, for Biedl's admirable monograph (*Innere Secretion*, Wien, 1910) completely reviews all work up to date.

[3] Elliott and Tuckett. This *Journal*, XXXIV. p. 351. 1906.

Roughly both lipoid and adrenalin content could be gauged by inspection of the cut surface of the gland after hardening it in a mixture of potassium bichromate solution and formalin (Orth's or Kohn's fluid). The fatty area is then visible as a white shell at the periphery, together with radiating streaks, as a rule, around the medulla: and the medulla takes a deep brown tint, varying patchily to a light yellow as exhaustion of its adrenalin progresses. The irregular distribution of the chromaffine reaction in the cells of a partially exhausted gland is very noticeable under the microscope, where exhaustion is generally found to occur earliest in the masses of cells adjacent to the largest veins.

But the histological method is inadequate. I consequently determined the actual amount of adrenalin that could be extracted from the glands after various phases of activity. The method used is capable of considerable accuracy. Briefly, it was as follows:

The suprarenals were excised, dissected clean, weighed, and each ground up with a little sand and Ringer's solution in a mortar. The extract was carefully washed out in a total volume of 15 c.c. This was boiled quickly, so as to avoid loss of fluid by evaporation, and filtered through glass wool. Sufficient extract, about 1·5 %, was thus obtained for several injections. The extract was not acidified, and the estimation was always made as soon as it had cooled. Precisely similar vessels were used for each of a pair of glands; and the figures obtained, right and left glands in a normal cat giving exactly equal results, prove that the method of extraction was relatively satisfactory.

The absolute quantity of adrenalin in the gland was perhaps represented also with fair accuracy by the results, for the loss of adrenalin in the coagulated gland substance and sand may have been approximately compensated for by the concentration of the extract in boiling: this amounted usually to 1 or 1·5 c.c. on 15 c.c., and it was not made good by the addition of an equivalent volume of Ringer's solution. The error due to this concentration, if considered alone, would make the adrenalin content of a gland appear about ·02 mgm. greater than it should be.

For the quantitative estimation of the adrenalin in the solution two methods are open, colorimetric being quite useless.

(1) The solution may be greatly diluted until the minimal strength is reached, which just affects some organ that reacts with great delicacy and certainty. The enucleated eyeball of the frog was suggested by Meltzer and used especially by Ehrmann. Its use has been often

criticised, and it is beyond doubt unsatisfactory. Best is the isolated uterus of the guineapig, as employed by Dale: but the chief value of this lies in its being an admirable test for the presence or absence of adrenalin. It is for qualitative rather than quantitative work.

(2) The actual concentration may be at once measured by intravenous injection into a cat. Under suitable conditions the resulting rise of blood-pressure varies directly with the amount of adrenalin injected. Some years ago I employed this method[1] with tolerable accuracy: the improvements suggested by Dale's experiments make it more reliable. After preliminary ether anæsthesia, the brain of a cat was destroyed by pushing a probe upward through the foramen magnum: a tracheal cannula was then inserted and artificial respiration commenced, both vagi being cut. The blood-pressure is now high, about 140 mm. of mercury. After a little delay, a long probe is then passed from the orbit, through the cranial cavity, and down the spinal canal to about the 4th thoracic segment. The blood-pressure soon falls to 40 or 50 mm.; and the circulatory system then will respond with the accuracy of a chemical balance to any dose of adrenalin. If only the medulla and brain are destroyed, the reflex machinery of the spinal cord often tends to prolong a blood-pressure rise induced by adrenalin and carry it on unduly in a series of rhythmic curves which hinder the estimation. On the other hand, if the cord be completely destroyed to the sacral end, the peripheral dilatation of the vessels is often so great that the heart ceases to beat, and in any case the blood-pressure rise caused by adrenalin becomes slow and irregular. A slight tone must, therefore, be present in the vessels for the reaction to be reliable. Any irregularity in the reactions is best dealt with by rejecting the animal and making a fresh preparation.

The injection was made into the external jugular vein by a cannula in connection with a burette of Ringer's solution.

It is necessary that the injections should be made as nearly as possible in equal times, and this was done by listening to a metronome beating seconds. The volume of solution containing adrenalin injected through the side needle was 1 c.c. in 5 seconds, which was at once

[1] This *Journal*, xxxii. p. 447. 1905. In a table of the maximum rises of blood-pressure attained by adrenalin under ether or urethane (*loc. cit.* p. 448), I was inclined to regard such height as the greatest which the muscles of a cat's circulation could attain. This was wrong. Adrenalin gives a rise to 300 mm. But the extreme stimulation of all the vaso-constrictor nerves and cardiac accelerators, caused by the passage of a narrow probe down the spinal cord, will raise the blood-pressure to 400 mm. in a cat free from anæsthetic after preliminary destruction of the brain.

washed through by 5 c.c. from the burette in the next five seconds. The injection fluid was simply at room temperature, and when introduced alone it did not affect the blood-pressure.

The curve of blood-pressure rise was inscribed on a kymograph, which was then turned back by hand, and the next injection made so that the curves should overlie one another. Identity of reaction requires that the curves should coincide in length as well as in height. As a standard solution any of the commercial preparations could be used. I preferred Höchst's synthetic suprarenin, ·1 %, which for injection was diluted to ·0025 %, so that 1 c.c. (·025 mgm.) gave a maximal rise of blood-pressure.

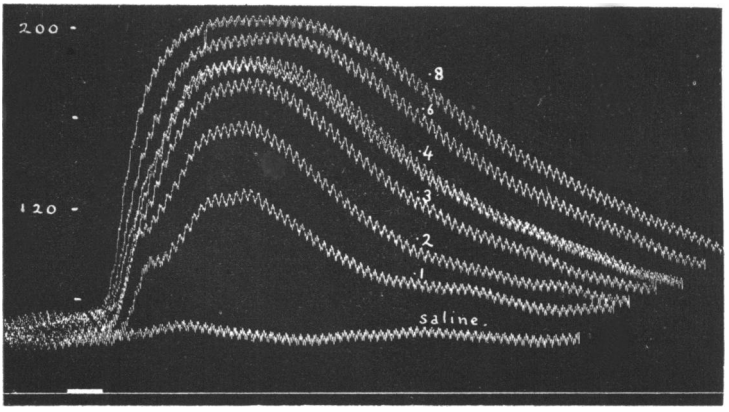

Fig. 1. Pithed cat. Gradation of response to increasing doses of a standard solution of suprarenin, ·0025 p.c. The injections were made in succession from the lowest curve upwards; after 0·8 c.c. again 0·4 c.c. was injected, and the resultant curve is seen to coincide very closely with that previously obtained with 0·4 c.c.

The subjoined curves (Figs. 1 and 2) will illustrate the progressive increase in amplitude of the curves as the dose of suprarenin is increased, and they show that there is surprisingly little fatigue in the reaction. No time for recovery need be allowed, so soon as the blood-pressure has fallen to its original level. When the blood volume has been increased by the injection of 50 c.c. Ringer, it is well to abstract about 30 c.c. of blood and wait a short time for recovery. Generally 1 c.c. of the extract was injected, then such amount of the standard, ·6 or ·8 c.c., with saline up to 1 c.c., as was thought likely to give a similar reaction. With one curve above and one below that of the extract, it was usually sufficient to deduce the exactly equivalent amount of the standard by

interpolation and not to try exactly to duplicate the curve. The first amount of the extract was then injected again, to test whether the reaction was satisfactory and corresponded exactly with the first. This it should do.

Several estimations can easily be made on the same cat, so that not only was each of a pair of glands assayed on the same animal, but also glands from four or five cats, that had been subjected to different conditions of experiment on the same day, could be contrasted with one another under the same conditions of assay. This gave full value to the

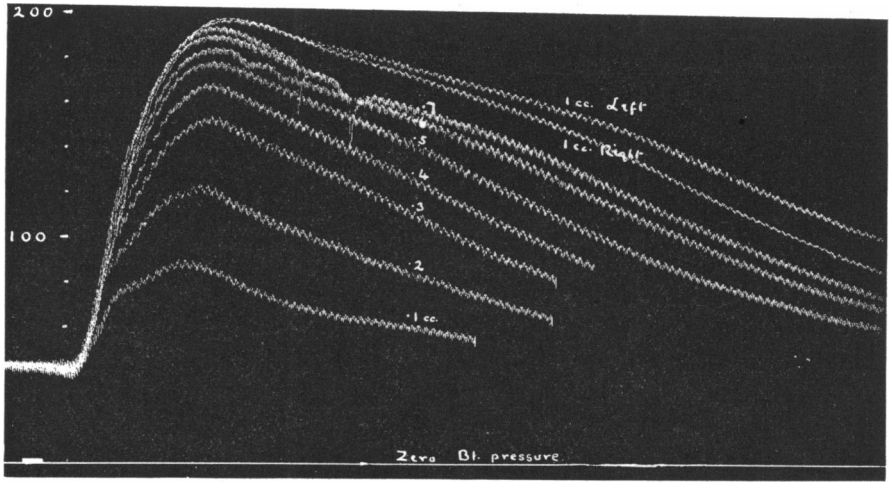

Fig. 2. A graded series of curves like the last, but with a slightly different type of reaction from the test cat. After 0·7 c.c. there were injected first 1 c.c. of the extract of the left suprarenal of another cat, and then 1 c.c. of an extract from the right gland. The two glands contained nearly equal amounts.

contrasting experiments, even if there were any doubt as to the absolute value of the adrenalin estimations; and it was an economy of working time. Under favourable conditions and by the exercise of some patience, the adrenalin content of a cat's gland could be assayed to an accuracy of ·01 mgm., and always, at any rate, to ·03 mgm. This form of adrenalin estimation naturally precluded any observations on the distribution of the cortical fat.

Normal glands.

In an earlier paper[1] I have given a series of weights of suprarenals from a number of cats, and remarked on the slight difference in weight between right and left glands, together with the considerable increase in size with bodily growth, especially in the female. These differences were seen to be mainly due to cortical growth, although there was also some increase of the medulla. The total adrenalin content varies much more widely than the size of the medulla, for it fluctuates greatly from time to time in the same animal: very roughly it is about one-thousandth of the weight of each gland.

In nearly all intact animals the residual adrenalin is exactly equal in the right and left glands.

The highest yields were always found in cats that had been in the laboratory a week or more, resting quietly each in a single cage and being well fed. For example:

(1) Good tempered cat, in stock one week: killed suddenly.
Right gland ·20 gm. = ·32 mgm. suprarenin.
Left gland ·195 gm. = ·32 ,, ,,

Recent admissions on the other hand were always sulky for a day or so, ready to snarl at their comrades, and very suspicious of their surroundings. In such, though their general bodily conditions might be good, the adrenalin value was always lower, *e.g.*

(2) Right gland ·21 gm. = ·15 mgm. suprarenin.
Left ,, ·22 gm. = ·14 ,, ,,

At various times 16 normals were examined, and only three of these gave a difference of as much as ·02 mgm. between the two sides. The assay results for an adult cat were on an average, weight of each gland ·2 gm., and adrenalin = ·22 mgm.

Effect of fright.

My first endeavour toward the analysis of pathological conditions was to examine the effect of fever alone without the complications introduced by microbic toxins. For this purpose I used the well-known pyretic drug β-tetrahydronaphthylamine hydrochloride. It failed to produce the desired effect. Two or three c.c. of a 2 % solution injected subcutaneously did not raise the rectal temperature of a cat by more

[1] Elliott and Tuckett. This *Journal*, xxxiv. p. 336. 1906.

than a degree, while it caused the most obvious and persistent excitation of certain plain "sympathetic" muscles. The pupils are dilated to the utmost, and the eyeball is protruded: the whiskers are set stiffly erect, and the hairs down the back and on the tail are all raised. At times there is a tendency to lacrymal secretion, and the animal salivates a little. The body muscles show no tremor, nor unsteadiness: but the cat presents all the external features and attitude of persistent, wide-eyed alarm. Such, too, is its psychological state. Left alone, it may cry at intervals: snarls and hisses greet any one who approaches the cage. Next day the effect of the drug has passed away; the cat regains its equanimity and eats freely. β-tetra in the cat, then, causes fear and stimulation of the sympathetic muscles, but not fever.

During its action, the suprarenal glands suffer partial loss of residual adrenalin. On account of the varying load of adrenalin, upon which emphasis has already been laid in respect of different cats in different emotional states, it is of little value to quote figures for a normal cat under the influence of the drug, for the exhaustion is not complete.

It was found that the exhaustion was affected by central impulses passing through the splanchnic nerves, and this provided a clear method of demonstrating the action.

Splanchnic innervation. In a series of cats the splanchnic nerves were cut. This was done through a lumbar incision without opening the peritoneal cavity. The major splanchnic was identified and dissected down to the semilunar ganglion: the latter was then hooked up and all the preganglionic nerves to it divided. The dissection needs to be thorough, lest the minor collateral strands that cross the aorta from the lumbar sympathetic, or even the minor splanchnic itself, escape section. No blood vessels were divided, and care was always given to preserve the great lymphatic vessels behind and above the semilunar ganglion. The suprarenal itself was not interfered with at all. Probably the nerves were all divided in their preganglionic course[1].

It will be seen from the subsequent results (cf. chiefly Exps. 10 and 21) that the mere dissection in itself did not affect the functions of the suprarenal gland. None the less, as it might be urged that harm was

[1] Nerve ganglion cells are always present in the medulla. Dogiel figures these (*Arch. f. Anat. u. Physiol.* p. 90, Fig. 8, *B.* 1894) as being definitely on the course of the numerous medullated nerves that lie in the medulla of the gland. Perhaps all the nerves external to the gland are preganglionic, and the glandular fibres have no cell stations in the semilunar ganglion.

done by cutting tissues so close to the suprarenal, in many of my experiments, where the cat was not required to live after the operation, the sympathetic nerves were divided within the thorax just before they pierce the diaphragm. The recognition of the nerves in this situation is even easier than in the abdomen, and both right and left trunks can be divided, if necessary, from an opening on one side of the thorax, since the contralateral trunk is easily seen when the thoracic aorta is raised from its bed. Section of the splanchnics in the following experiments means division below the diaphragm, except where it is specially stated to have been done within the thorax.

The vagus has no direct anatomical connection with the suprarenals, and consequently experiments were not made directly to test its control. But in the course of my various experiments no difference was ever observed to depend upon the chance whether the vagi were cut or uncut.

After the operation the animals soon regained perfect health, and their suprarenals in consequence were always loaded with adrenalin to a high figure. Mere section of the nerves does not affect the adrenalin load in a quiet animal. Examples are:

(3) Left splanchnics cut 1 day.
Right gland ·13 gm. = ·32 mgm. suprarenin.
Left ,, ·13 gm. = ·33 mgm.

(4) Left splanchnics cut 2 days.
Right gland ·265 gm. = ·37 mgm.
Left ,, ·27 gm. = ·37 mgm.

(5) Left splanchnics cut 11 days.
Right gland ·12 gm. = ·17 mgm.
Left ,, ·11 gm. = ·17 mgm.

(6) Right splanchnics cut 14 days.
Right gland ·2 gm. = ·30 mgm.
Left ,, ·2 gm. = ·30 mgm.

The changes associated with *pregnancy* do appear to make some call upon the suprarenals, for the glands are larger in the multiparous female than in the male. Yet a healthy parturition, in itself, does not exhaust them.

(7) Left splanchnics cut 11 days.
Ten days after the operation she gave birth to two kittens, apparently without any trouble. Killed 20 hours after parturition, when she was contentedly suckling the kittens.
Right gland ·25 gm. = ·30 mgm.
Left ,, ·25 gm. = ·30 mgm.

However, many conditions can be induced in which a differential loss of adrenalin occurs, and one means to that end is the subcutaneous injection of β-tetra with its resultant fright.

(8) Right splanchnics cut 15 days.
2 c.c. 2 % β-tetra injected 8 hours, and 2·5 c.c. 4 hours before death. Moderately angry. Killed suddenly.
Right gland ·23 gm. = ·30 mgm.
Left ,, ·21 gm. = ·15 mgm.

(9) Left splanchnics cut 11 days.
3 c.c. β-tetra 24 hours before death. Very angry. Killed suddenly.
Right gland ·22 gm. = ·07 mgm.
Left ,, ·22 gm. = ·19 mgm.

(10) Left major splanchnic cut 18 days.
3 c.c. β-tetra 24 hours before death. Very angry. Killed in 15 minutes by 1·2 mgm. strychnine.
Right gland ·250 gm. = ·18 mgm.
Left ,, ·235 gm. = ·19 mgm.
This illustrates what was seen in other cases, namely that section of the major splanchnic alone did not suffice to prevent exhaustion of the gland.

(11) Right splanchnics cut 13 days.
5 c.c. β-tetra 7 hours before death. Killed. Glands examined histologically. Fat was equally distributed in the usual zones in each, but the left gland contained absolutely no chromaffine substance, whereas the right took a deep brown stain.

This loss of residual adrenalin was, therefore, to be regarded as the result of central nervous impulses, and not caused by direct peripheral stimulation of the gland cells. It was not due to fever, but might have been associated either with the emotion of alarm, or with the excitation of the hair and other sympathetic muscles. Jonnescu[1] emphasised the fact that the general stimulating action of the drug is on muscles with sympathetic innervation and not on gland cells; and he suggested, from degenerative section experiments, that the seat of its action is partly central, and partly peripheral. The latter is more or less true. After excision of the superior cervical ganglion, the effects on the denervated pupil are certainly almost as full as on the normal eye; but this may be a response to the adrenalin liberated from the suprarenals. No excitation results from direct application of the drug to the cells of the superior cervical ganglion. Still the general sympathetic excitation is slight: injected intravenously it produces, in small doses, only a slight rise of blood-pressure, and a rapid fall with bigger amounts: nor is there any manifest rise when it is injected subcutaneously. Hence it does not seem very probable—though the

[1] *Arch. f. exp. Path. u. Pharm.* LX. p. 345. 1909.

hypothesis cannot be excluded—that the adrenalin exhaustion ought to be regarded as a discharge directly required in consequence of the prolonged excitation of an area of muscle with sympathetic innervation.

There remains the emotional alarm, a feature very prominent in the cat, much less obvious in the rabbit and guineapig[1], where it was, however, noticed by Pembrey and Mutch[2]. This might be either an emotion of central origin, or, on James' theory, the mental expression of the impulses generated by the drug's continuous peripheral excitation of the muscles of emotional expression. An experiment somewhat similar to Sherrington's[3], was made to test this. The spinal cord of a cat, which had been previously proved to give a full emotional reaction to β-tetra, was transected at the first thoracic segment. Ten days later 2·5 c.c. of 2 % β-tetra were injected subcutaneously. The usual peripheral reaction was seen, and the animal, which had previously been peaceful, became very angry and bit its attendant.

Apparently, therefore, the emotion is centrally excited; and it seemed possible that it was this fright alone which led directly to the exhaustion of the suprarenal as an immediate means towards the expression of this emotion.

At Prof. Cushny's suggestion I made use of another drug which terrifies cats, *morphia*. Twenty mgm. of this impels a cat into ceaseless, wild, disordered movements that strongly suggest their origin in pressing hallucinations of dread. The animal gives no cry; it does not attack those who approach it; and, while its pupils are dilated, it evinces no other phenomena of peripheral sympathetic excitation. Yet the exhaustion of adrenalin via the splanchnic nerves is even more marked than with β-tetra, where, on the other hand, the peripheral stimulation is greater.

(12) Left splanchnics cut 9 days.
Morphia 20 mgm.: cat killed 8 hours later.
Right gland ·205 gm. = ·02 mgm.
Left ,, ·200 gm. = ·15 mgm.

[1] The pigeon does not respond by any indication of alarm, nor are its feathers displaced. In my own forearm, where adrenalin is quite effective, β-tetra produces no pilomotor effect and no vaso-constriction. I never used a large enough injection in myself to cause any sensation of alarm, being to some extent deterred from doing so by the curious fact that subcutaneous injection of β-tetra invariably causes acute gastric ulcers in the guineapig.

[2] This *Journal*, XLIII. p. 123. 1911.

[3] *Integrative action of the Nervous System*, p. 260. London, 1909.

(13) Left splanchnics cut 17 days.
Morphia 20 mgm.: killed 6 hours later. (Cf. Fig. 3.)
Right gland ·195 gm. = ·07 mgm.
Left ,, ·190 gm. = ·22 mgm.

(14) Left splanchnics cut 40 days.
Morphia 30 mgm.: killed 8 hours later.
Right gland ·205 gm. = ·02 mgm.
Left ,, ·210 gm. = ·12 mgm.

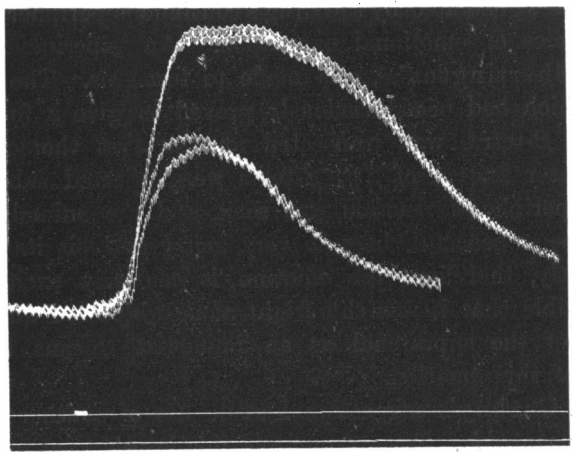

Fig. 3. From Exp. (13). Left splanchnics cut, and right gland exhausted by fright of morphia. Labelling the curves A, B, C, D from the topmost downwards, they correspond respectively to

(A) 1 c.c. of left gland,
(B) 0·6 c.c. of ·0025 % suprarenin,
(C) 1 c.c. of right gland,
(D) 0·2 c.c. of ·0025 %,

and they were injected in the order C, A, D, B.

As a control to this, strychnine was injected in successive small doses of ·4 mgm.: the result was a little muscular rigidity, but no alarm. A final dose of ·6 mgm. suddenly killed the cat in ten minutes.

(15) Left splanchnics cut 17 days.
Strychnine 1·8 mgm. in 6 hours. Died.
Right gland ·2 gm. = ·26 mgm.
Left ,, ·2 gm. = ·26 mgm.

There can, then, be no doubt of the fact that a differential exhaustion of the glands, when the splanchnics have been divided on one side, is caused by morphia and by β-tetra, drugs which have the common action of exciting the cat to emotional alarm. Experiments will be described in subsequent pages, which tend to justify the view

taken, that this exhaustion is directly due to the fright caused. The most direct method of analysis would be that of inducing emotional fear at once, as by vexing the cat with a dog. This I have not done. But evidence of that nature is supplied by the experiments of Cannon and de la Paz[1] in which, by a very delicate and ingenious method, they showed that the emotion of anger or fear is associated with the appearance of adrenalin in the blood from a cat's suprarenal vein.

Rise of blood-pressure. The results with β-tetra could be explained on either of two views:

(*a*) That a large area of sympathetic muscle is thrown into action, in part directly by the drug and in part indirectly by the nervous system, and that the suprarenal gland secondarily receives a call through the splanchnic nerves to contribute its help to that peripheral action.

(*b*) That the whole machinery of sympathetic musculature and of the suprarenal glands may be at once and simultaneously excited by a universally distributed impulse, as in emotional alarm, the call on the suprarenal being then made directly and urged whether the peripheral musculature responds or not.

Emotional alarm could be present with either (*a*) or (*b*), though the latter has in the preceding pages been taken as the provisional explanation. The hypotheses at once suggest further experiments, in which the excitation of the sympathetic musculature shall be caused independently of alarm. The simplest is that of producing a general and prolonged rise of blood-pressure. Stimulation of the central end of a large nerve, such as the cut sciatic, does not cause a big rise. I therefore endeavoured to reproduce the conditions of cerebral hæmorrhage in man, in which a prolonged rise in blood-pressure is often caused by the injurious presence of the outpoured blood.

A cat was pithed by pushing a sharp stilette through the foramen magnum and forwards to the frontal lobes, where a lateral movement transects the crura cerebri. If the animal's head be fully flexed during this operation, the instrument will pass through the cerebellar peduncles above the medulla, so that independent respiration is preserved. The blood-pressure, after a transient enormous rise (associated with sweating from the pads), falls to a high level of 140 or 150 mm.: both vagi are then divided, and the splanchnic nerves cut on one side. The cat is covered up on a warm box, ultimately killed, and the adrenalin content of the two suprarenals assayed. Exhaustion

[1] *Amer. Journ. Physiol.* XXVIII. p. 64. 1911.

occurs quickly on the side which is still in connection with the spinal cord.

(16) Pithed 6 hours. Natural respiration throughout. Vagi and left splanchnics cut. Blood-pressure slowly fell from 170 to 110 mm. No rise of temperature. Glycosuria.

Right gland ·12 gm. = ·03 mgm.
Left ,, ·125 gm. = ·19 mgm.

(17) Pithed 4 hours. Left splanchnics cut. Natural respiration throughout. Blood-pressure 140 to 150 mm.

Right ·22 gm. = ·11 mgm.
Left ·20 gm. = ·23 mgm.

(18) Left splanchnic nerves cut 40 days.
Pithed 4 hours: artificial respiration needed. Vagi cut. Blood-pressure for 1 hour at 110, for 3 hours at 80 to 60 mm.

Right ·24 gm. = ·15 mgm.
Left ·23 gm. = ·30 mgm.

The same effect was also observed when the cerebral hemispheres alone were destroyed by pushing the stilette through the temporal fossa immediately across the crura cerebri, and without direct damage of the brain structures below the tentorium.

(19) Transtemporal pith. Artificial respiration. Vagi and left splanchnics cut. Blood-pressure 140 for 3½ hours. Slight glycosuria: no fever.

Right ·25 gm. = ·19 mgm.
Left ·27 gm. = ·32 mgm.

(20) Pithed 6 hours. Natural respiration. Left splanchnics cut. Blood-pressure 160 to 140 mm. Glands hardened in Orth's fluid.

Right colourless.
Left full chromaffine tint. Fat equal in each.

To prove that the dissection around the semilunar ganglion did not hinder loss of adrenalin from the gland of that side by interference with its circulation, the following experiment was made.

(21) Pithed 4 hours. Natural respiration: vagi cut. Blood-pressure 160 to 140. Right splanchnics cut. Left splanchnics fully dissected out, but not cut.

Right ·26 gm. = ·34 mgm.
Left ·25 gm. = ·04 mgm.

Lastly, the sympathetic nerves were cut within the thorax, so as to avoid all chance of interference with the tissues around the suprarenal gland.

(22) Pithed 5 hours. Left splanchnics cut within thorax. Natural respiration re-established.

Right ·165 gm. = ·11 mgm.
Left ·14 gm. = ·26 mgm.

From these, and other experiments with invariably the same results, it was certain that the damage to the brain led to exhaustion of the suprarenal that was still in nervous connection with the spinal cord. But there still remained unsettled the distinction between the possible explanations (*a*) and (*b*); for the exhaustion was accompanied by a persistent rise of blood-pressure and steady constriction of the muscles of the blood vessels.

With the hope of removing this vasoconstriction I injected into the veins β-iminazolylethylamine, the histamine which Dale and Laidlaw[1] have shown to be so powerful a depressor of the cat's systemic blood-pressure, while it either leaves untouched or stimulates the known sympathetic glandular nerves. The cat was pithed, β-i injected so as to reduce the blood-pressure to a low value, and then the left splanchnics cut. Exhaustion of the contralateral suprarenal still resulted.

(23) Pithed: natural respiration: blood-pressure 170 mm. β-i, 0·6 mgm. injected: blood-pressure fell to 60. Left splanchnics cut. Killed 2 hours later, blood-pressure being about 40 mm. all the last hour. No glycosuria.
Right ·18 gm. = ·03 mgm.
Left ·14 gm. = ·16 mgm.

(24) Pithed 4 hours. β-i, in all 2·3 mgm. of the base. Blood-pressure fell from 150 to 50. Left splanchnics cut. The vaso-constrictors were not paralysed, for crushing the leg bones caused an immediate reflex rise of pressure from 50 to 160.
Right ·15 gm. = ·01 mgm.
Left ·15 gm. = ·11 mgm.

Intravenous injection of β-i, therefore, does not serve to make the desired distinction. During its action the blood-pressure is very low, but the vaso-constrictors are not fully paralysed, and the nervous exhaustion of the suprarenal proceeds as usual. As will be shown later, the drug does not directly excite the gland cells to excretion.

This view, that cerebral irritation may directly excite the suprarenals, is not a new one. André Mayer[2] elaborated Blum's[3] suggestion that the glycosuria of Bernard's "diabetic puncture" might be caused by the splanchnics playing on the suprarenals, and liberating adrenalin which in its turn would act upon the liver to produce sugar. Nishi[4] was guided by a similar opinion, when he showed that the subcutaneous injection of diuretin failed to cause glycosuria in a rabbit after excision of its suprarenals. Cannon[5] and his collaborators further proved that emotional fear led to glycosuria in cats, but

[1] This *Journal*, XLI. p. 318. 1910–1911.
[2] *C. R. Soc. de Biol.* p. 1123. 1906; and p. 219. 1908.
[3] *Pflüger's Arch.* XC. p. 617. 1902.
[4] *Arch. f. exp. Path. u. Pharm.* LXI. p. 401. 1909.
[5] *Amer. Journ. Physiol.* XXIX. p. 280, and p. 274. 1911.

failed to do so when the suprarenals had been previously excised. The sole contrary evidence is that of Wertheimer and Battez[1], who state that they were able to cause glycosuria in cats by the Bernard puncture after removal of the suprarenals. The bulk of evidence is in favour of the view that brain injury or excitation discharges the suprarenals, and so may produce moderate glycosuria.

Sugar always appeared in the urine of my pithed cats, though its amount was much reduced in the cases where β-i had been injected with a consequent fall of blood-pressure and diminution of urinary secretion.

Effect of anæsthetics and of other drugs.

From the experiments already cited, it appeared probable that the alarm in a cat attendant upon the induction of anæsthesia by ether or chloroform would lead to some exhaustion of residual adrenalin. But there was no reason to suppose that the exhaustion would proceed subsequently while the brain was in a state of deeper anæsthesia. Such, however, was found to be the case.

Ether.

(25) Ether 6 hours: left splanchnics cut. Blood-pressure 160 to 140.
Right gland ·23 gm. = ·11 mgm.
Left „ ·23 gm. = ·22 mgm.

(26) Female, 2700 gms., which had kittened a day or two previously. Ether 3 hours. Left splanchnics cut: blood-pressure 140, but 50 in last hour.
Right ·45 gm. = ·20 mgm.
Left ·45 gm. = ·45 mgm.

(27) Left splanchnics cut 9 days.
Light ether 5 hours. No blood-pressure taken, so as to avoid all operative interference with the animal's tissues.
Right ·28 gm. = ·13 mgm.
Left ·25 gm. = ·21 mgm.

Other experiments were made with a slight variation from the usual type. A gland extract made in the ordinary way, and not acidified, was found to lose strength slowly on standing at room temperature—in four experiments the solution lost in six hours on an average ·04 mgm. or roughly 20 %. An excised gland kept on ice for six hours lost practically no adrenalin; whereas one kept at room temperature (17°) in a moist chamber lost about 30 %. For example, the glands were both excised from a newly killed cat: that of the right side was at once assayed, ·15 gm. = ·22 mgm.: the left was kept at 17° C. for five hours and then extracted, ·16 gm. = ·15 mgm.

Since the glands on each side normally contain exactly similar amounts of adrenalin, and since an excised gland kept on ice suffers

[1] *Arch. internat. de Physiol.* p. 363. 1910.

very slight loss of adrenalin in a few hours, the following experiments were justified as illustrating the nervous control of adrenalin loss under ether.

(28) **Ether. Right gland at once excised: left gland intact. Ether continued for 6 hours. Blood-pressure 110 to 90.**

Right ·2 gm. = ·26 mgm.

Left ·2 gm. = ·07 mgm. (Cf. Fig. 4.)

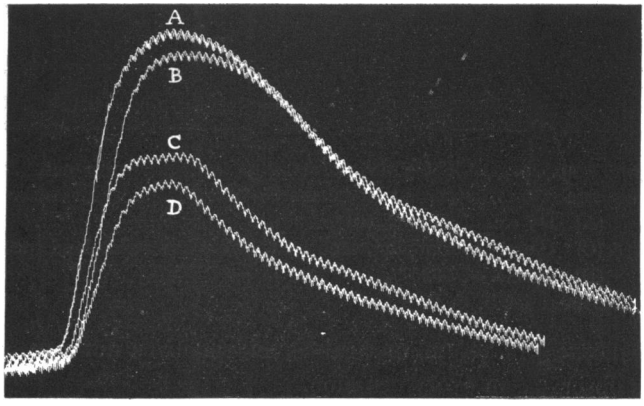

Fig. 4. From Exp. (28). Right gland excised, and left splanchnics cut. Ether anæsthesia for 6 hours, which exhausted left gland. Curves A, B, C, D from above downwards are respectively

(A) 1 c.c. of extract of right gland,
(B) 0·6 c.c. of ·0025 % suprarenin,
(C) 0·2 c.c. of ·0025 %,
(D) 1 c.c. of left gland.

Injected in the order B, D, C, A.

The exhaustion of the gland left in the cat could be largely prevented by section of the splanchnic nerves.

(29) **Ether. Left gland excised. Right splanchnics cut. Ether continued for 5 hours. Blood-pressure 110 to 130. Animal then killed.**

Right ·16 gm. = ·12 mgm.

Left ·14 gm. = ·11 mgm.

(30) **Ether. Left splanchnics cut, and right gland excised. Ether continued for 7 hours. Blood-pressure 140 to 130.**

Right ·26 gm. = ·23 mgm.

Left ·30 gm. = ·23 mgm. (Cf. Fig. 5.)

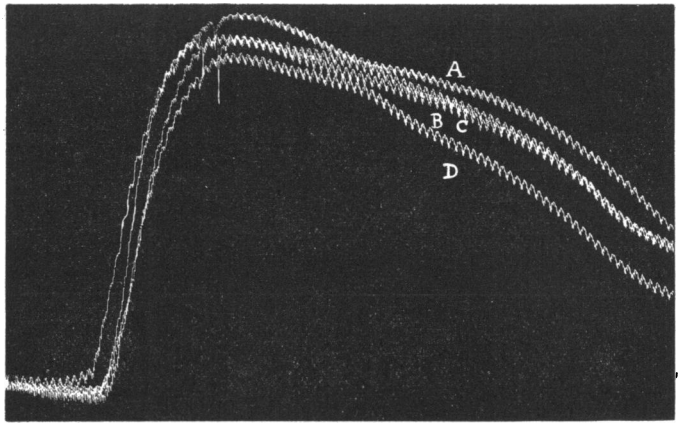

Fig. 5. From Exp. (30). Right gland excised, and left splanchnics cut. Ether anæsthesia continued for 7 hours, but no exhaustion of left gland. Curves are

(A) 0·7 c.c. of ·0025 % suprarenin,

(B) & (C) Closely overlapping, each 1 c.c. of left and right gland successively,

(D) 0·5 c.c. of ·0025 %.

Injected in the order B, C, D, A.

The exactness of this numerical coincidence was not a mere chance, for it was observed on every occasion.

(31) Ether. Left splanchnics cut within thorax. Right suprarenal excised and placed in ice chest. Ether continued for 5 hours. Blood-pressure finally 140 mm.

Right ·23 gm. = ·27 mgm.
Left ·22 gm. = ·27 mgm.

Similar results were obtained with other anæsthetics.

Chloroform. Anæsthesia is induced much more quickly than with ether, and there is less struggling and holding of breath up to a stage of partial asphyxia. But the exhaustion of the suprarenal is fully as great as with ether, and is effected in the same way through the splanchnic nerves.

(32) Chloroform 5½ hours: left splanchnics cut.

Right ·185 gm. = ·08 mgm.
Left ·175 gm. = ·21 mgm.

(33) Chloroform 5 hours: left splanchnics cut within thorax, which was then closed and natural respiration re-established.

Right ·19 gm. = ·15 mgm.
Left ·18 gm. = ·26 mgm.

(34) Left splanchnics cut 12 days by previous operation. Chloroform 2¾ hours. No blood-pressure taken.

Right ·22 gm. = ·17 mgm.
Left ·20 gm. = ·24 mgm.

(35) Chloroform. Left splanchnics cut within thorax. Right suprarenal excised. Chloroform continued 5 hours, and cat killed when blood-pressure was 130 mm.

Right ·23 gm. = ·21 mgm.
Left ·23 gm. = ·21 mgm.

Urethane. Subcutaneous injection of this narcotic can be effected without much alarm of the cat, which passes slowly and drowsily into a state of unconsciousness. So the excitement of the first stages of anæsthesia by the volatile anæsthetics is avoided. Still the exhaustion through the nerves appears.

(36) Urethane, 18 c.c. of 25 % subcutaneously. Left splanchnics cut 1½ hours later, when fully narcotised. Killed 4½ hours after this. Was perfectly quiet.

Right ·12 gm. = ·07 mgm.
Left ·11 gm. = ·13 mgm.

(37) Urethane. Left splanchnics cut 2 hours later. Killed 6 hours after this, when blood-pressure was 106.

Right ·185 gm. = ·11 mgm.
Left ·189 gm. = ·28 mgm.

Pilocarpine. It would be of great interest to prove that some drug has power directly to stimulate the suprarenal medullary cells to excretion of adrenalin, for then the apparent general action of the drug on other tissues of the body would be complicated by the reaction secondary to the adrenalin liberated[1].

I have made several experiments upon this point, but failed to find proof that pilocarpine influences the adrenalin load in any way. Tscheboksaroff[2] also could find no evidence that pilocarpine excites secretion from the suprarenals.

(38) Ether 4 hours: left splanchnics cut. Pilocarpine in successive doses of 5 mgm. up to 20 mgm. Very free secretion of saliva, tears, and sweat.

Right ·26 gm. = ·17 mgm.
Left ·26 gm. = ·26 mgm.

Here the only exhaustion was the ordinary effect produced under ether through the splanchnic nerves: the left gland with cut nerves retained a big load of adrenalin. Absence of evident exhaustion does not exclude some brief stimulus to excretion: for it will be shown later in this paper that faradisation of the splanchnic nerves does discharge adrenalin into the blood, but yet fails to produce very obvious exhaustion of the residual adrenalin.

[1] Cf. Dale and Laidlaw. *Proc. Physiol. Soc.* This *Journal*, XLIV. p. xii. 1912.
[2] *Pflüger's Arch.* CXXXVII. p. 59. 1910-1911.

(39) Ether 2½ hours: right splanchnics cut: left dissected out, but not cut. Pilocarpine in all 30 mgm. Profuse secretion of saliva, and twitching of body muscles.

Right ·195 gm. = ·30 mgm.
Left ·19 gm. = ·24 mgm.

In neither of these assays was allowance made for the small amount of pilocarpine that might be present in the suprarenal glands, for this would probably be the same in each, and could not affect the contrast result.

Physostigmine. This drug, according to the experiments of Tscheboksaroff on dogs, does increase the output of adrenalin even after section of the splanchnics. I could not find any trace of consequent exhaustion in cats.

(40) Ether for 3 hours. Left splanchnics cut within thorax. Physostigmine in successive doses up to total of 14 mgm. Fair secretion of saliva: bodily twitchings: blood-pressure slowly sank to very low level.

Right ·17 gm. = ·09 mgm.
Left ·18 gm. = ·15 mgm.

(41) Ether. Left splanchnics cut within thorax. Physostigmine 9 mgm. Died in 1½ hours, with very low blood-pressure.

Right ·19 gm. = ·08 mgm.
Left ·20 gm. = ·23 mgm.

Histamine. This poison, β-iminazolylethylamine, has been discussed earlier in the paper. It has no direct exhausting action on the medullary cells.

(42) Ether. Right suprarenal excised and placed on ice: left splanchnics cut within thorax. β-i in successive doses of ·5 mgm. of the base, up to total of 4 mgm. in 3 hours.

Right ·2 gm. = ·17 mgm.
Left ·2 gm. = ·15 mgm.

Pituitary gland extract. There are some hazy views current as to the interaction of the ductless glands, and therefore it is desirable to know whether pituitary extract can stimulate excretion of adrenalin from the medullary cells, the more so inasmuch as its direct action on some gland cells has been illustrated by Ott's[1] discovery that it stimulates the mammary gland to rapid secretion.

(43) Ether 4½ hours. Left splanchnics cut within thorax. Pituitary extract, Burroughs' and Wellcome's 20 % preparation, given in successive doses up to total of 3 c.c.

Right ·35 gm. = ·22 mgm.
Left ·32 gm. = ·32 mgm.

This is practically the same differential result that would have been seen with the administration of ether alone for 4½ hours. A second experiment gave a similar result.

[1] Cf. full analysis by Schäfer and Mackenzie. *Proc. Royal Soc.* B, p. 16. 1911: and *Quart. Journ. Exp. Physiol.* IV. p. 305. 1911.

Adrenalin. The intravenous injection of this substance in large quantities does not appear to influence either storage or loss of adrenalin from the suprarenals. There is certainly no direct action on the gland.

(44) Ether. Right splanchnic cut within thorax and left suprarenal excised. Adrenalin then injected into jugular vein in successive doses of ·2 mgm. until total of 3·5 mgm. was reached in 4 hours. Blood-pressure rose generally to 220 mm.

Right ·205 gm. = ·23 mgm.
Left ·20 gm. = ·23 mgm.

The loss when the splanchnic nerves are uncut, is much the same as would be seen if the cat were left under similar conditions of ether anæsthesia and without the injection of adrenalin. The adrenalin has no apparent effect in saving the gland from exhaustion.

(45) Ether. Left splanchnics cut within thorax. Adrenalin injected to total of 3·5 mgm. in 3 hours. Blood-pressure rose at first to 350 mm., and later to 240. In this, as in the preceding case, numerous small hæmorrhages were caused in the cortex of the glands.

Right ·16 gm. = ·03 mgm.
Left ·15 gm. = ·15 mgm.

A statement of mine in an earlier paper[1], that the injection of adrenalin discharges the medullary cells, was a mistake due to ignorance of the loss under simple ether anæsthesia and experimental interference with the animal's tissues, conditions in themselves sufficient to produce the changes which I had attributed to the adrenalin.

Diphtheria toxin. Many observers have remarked on the hæmorrhagic congestion produced in the suprarenal glands of rabbits and guineapigs by the fatal action of microbic poisons, this being especially noticeable in death caused by diphtheria toxin. The view has in consequence often been urged that one function of the suprarenal may be to neutralise such toxins. For this the sole evidence is an old experiment of Walter Myers[2], that cobra venom is rendered harmless when triturated with suprarenal gland cells. This particular result, however, might be ascribed to the active oxidase in the suprarenal. There is no reason at all for believing that microbic toxins can be neutralised by an action of suprarenal cells, whether of the cortex or medulla. Noon[3] showed this with regard to diphtheria toxin, and the fact has been confirmed by Ritchie and Bruce[4], who added the

[1] This *Journal*, XXXII. p. 427. 1905.
[2] *Brit. Med. Journal*, p. 946. 1898.
[3] This *Journal*, XXXIV. p. 332. 1906.
[4] *Journal Exp. Physiol.* IV. p. 127. 1911.

supplementary observation that diphtheria toxin in its turn does not exert any destructive action on adrenalin.

None the less the relationship of the toxins to the suprarenals might conceivably be a close one, namely this, that they are not destroyed by the gland, but that they destroy the animal largely through its glands, throwing them out of action and so inducing circulatory depression and death.

Such a view would be supported by the observation of many workers, especially of the French school, that the suprarenals of guineapigs killed by various infections are emptied of adrenalin and often congested, as particularly with diphtheria toxin. And it would embrace my cases of various septic fevers in man, where the adrenalin load is quickly lessened and the cortical lipoid vanishes at once. But the view would postulate a complete exhaustion of the adrenalin that death might ensue: and the exhaustion is not complete. Ritchie and Bruce, indeed, do describe a complete exhaustion by diphtheria toxin in the guineapig. But it certainly does not occur in the cat, nor in man.

(46) Diphtheria toxin, ·15 c.c., injected subcutaneously. Cat died in 40 hours. Glands, which were a little congested, assayed 12 hours after death.
Right ·21 gm. = ·14 mgm.
Left ·21 gm. = ·15 mgm.

This animal had been in stock some time, and its glands should have contained probably ·25 mgm. Some loss had, therefore, occurred over and beyond that due to post mortem changes in the 12 hours preceding their analysis. But the loss was much too slight to justify a belief that the animal succumbed to lack of adrenalin from its suprarenals. That the output of adrenalin from the glands can be maintained up to the time of death, and that the congestion does not simply lock it up inaccessibly within the gland, is proved by the subjoined experiments.

(47) Left splanchnics cut 32 days. Diphtheria toxin ·59 c.c. subcutaneously. Death in 17 hours. Glands equally and markedly congested: assayed at once.
Right ·27 gm. = ·04 mgm.
Left ·23 gm. = ·19 mgm.

(48) Left splanchnics cut 34 days. Diphtheria toxin, ·18 c.c., subcutaneously. Death in 30 hours. Glands assayed 3 hours later. Both slightly and equally congested.
Right ·26 gm. = ·04 mgm.
Left ·27 gm. = ·22 mgm.

(49) Left splanchnics cut 24 days. Diphtheria toxin, ·24 c.c., subcutaneously. Death in 38 hours. Glands assayed at once. (Cf. Fig. 6.)
Right ·35 gm. = ·02 mgm.
Left ·32 gm. = ·20 mgm.

(50) Left splanchnics cut 24 days. Diphtheria toxin, ·12 c.c. Death in 50 to 54 hours. Glands assayed about 4 hours after death.
Right ·23 gm. = ·03 mgm.
Left ·215 gm. = ·15 mgm.

(51) Left splanchnics cut 24 days. Diphtheria toxin, ·09 c.c., died in 70 hours. Glands congested, so as to resemble bluish red plums: assayed at once.
Right ·20 gm. = ·06 mgm.
Left ·19 gm. = ·15 mgm.

In these last five cats, which had been operated on, and were living quietly and happily in the laboratory, the adrenalin load of the glands should have been high. A slight loss occurred on the decentralised side, and much greater exhaustion on the side with nerves still intact. Soon after the injection, the animal refused food and moped. A similar period of moping would produce somewhat similar exhaustion in an

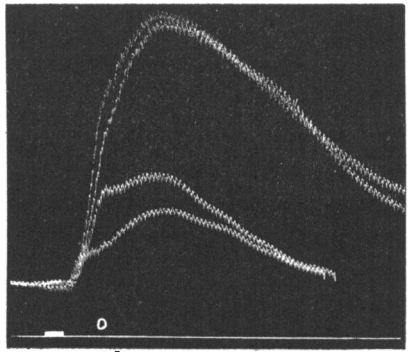

Fig. 6. From Exp. (49). Left splanchnics cut. Death by diphtheria toxin. Right gland alone exhausted. Curves are
(A) 0·6 c.c. of ·0025 % suprarenin,
(B) 1 c.c. of left extract,
(C) 0·1 c.c. of ·0025 %,
(D) 1 c.c. of right extract.

otherwise healthy cat, doing so by impulses playing on the glands through the splanchnic nerves. The exhaustion caused by diphtheria poisoning seems to be of this nature. It is mainly produced through the splanchnic nerves, and only to a slight degree by a direct action of the poison on the glands: and probably it is an expression of the efforts made by the animal to combat the fall of blood-pressure and other changes due to the action of the poison elsewhere. In brief, the adrenalin exhaustion is secondary, an expression of the cat's struggle for life: it is not a primary factor leading to death. In respect of the cortex there is no conspicuous difference between the decentralised and the other gland. Each shows spreading of the lipoid, though no longer doubly refractive, more widely through the cortex, and cloudy degeneration of the cells.

DIRECT STIMULATION OF THE SPLANCHNIC NERVES.

The method of determining the residual content of adrenalin, after section of the nerves on one side, proves beyond doubt that the splanchnic nerves influence the amount of adrenalin in the suprarenal glands.

Accepting Dogiel's account of the anatomical connection of the splanchnic nerves with the medullary cells, and also the observation made first by Cybulski, 1896, and since confirmed by many others, that adrenalin appears in the blood of the suprarenal veins, several workers have sought to give a clear proof of the obvious deduction, namely that the splanchnics should control the excretion of adrenalin from the glands. All have attempted this directly, by electrical stimulation of the splanchnic nerves and analysis of the outgoing venous blood.

Biedl's[1] earliest experiments suggested that the splanchnics carried vaso-dilator fibres to the glands, but could not demonstrate any increased excretion of adrenalin. Dreyer[2], however, obtained positive results with dogs. So, too, did Tscheboksaroff[3] in a very clear series of experiments, though he observed that after stimulation the gland on the stimulated side yielded a more potent extract, that is contained more adrenalin, than that of the other side. Waterman and Smit's[4] observations on rabbits are too uncertain to require discussion. So the direct proof of the nervous action, by faradisation of the splanchnic nerves, rests upon the results reported by Dreyer and Tscheboksaroff with dogs, and those recently by Asher[5] with rabbits.

Oddly, I have never succeeded in demonstrating more than a very slight loss in cats, when using the method of measuring the residual adrenalin. The effect of faradising the nerve directly is certainly much less than that caused indirectly through the machinery of central nervous control. Consequently, when a cat is kept under ether and the cut splanchnics faradised on one side, the contralateral gland ultimately is found to be the more exhausted. This result met me when first I tried stimulation of the splanchnic nerves, and it seemed inexplicable until later the reflex exhaustion under ether itself was analysed and found to be the cause of the paradoxical effect. Tscheboksaroff also observed it, though he explained the contrast by ipsilateral anabolism rather than contralateral katabolism.

[1] *Pflüger's Arch.* LXVII. p. 443. 1897.
[2] *Amer. Journ. Physiol.* II. p. 203. 1899.
[3] *Pflüger's Arch.* CXXXVII. p. 59. 1910–11.
[4] *Ibid.* CXXIV. p. 198. 1908.
[5] *Zntrlb. f. Physiol.* XXIV. p. 927. 1910.

I have made ten experiments, in which the splanchnic nerves were cut on both sides, so as to avoid the central effects of ether, and in which electrical stimulation was applied to the nerves of one side either above or below the diaphragm.

It should be remarked that when the sympathetic nerves were stimulated within the thorax, the main trunk was used for convenience of its length and consequently the preganglionic fibres, not only of the splanchnics but also of those running for some distance down the lumber sympathetic chain, were excited so that erection of hairs over the rump was caused. This did not introduce any serious error into the various experiments.

Faradisation was used for from three to seven hours, periods of stimulation for a few minutes alternating with those of rest, and the blood-pressure being always observed to make sure of the potency of the stimulus. The effect on the glands was very slight.

For example:

(52) Ether for 8 hours. Both splanchnics cut within thorax: right faradised for 7 hours, 7 minutes on and 3 minutes off. Even at the end of the experiment stimulation of the splanchnic caused the blood-pressure to rise from 80 to 110 mm.

Right ·25 gm. = ·21 mgm.
Left ·25 gm. = ·32 mgm.

When, instead of faradisation, rhythmic stimuli were thrown in at the slow rate of one a second, the effect was still less.

Nor was any better effect seen when the nerve was faradised continuously for a period of two hours: the loss then, indeed, was almost inappreciable.

On *dogs* I have made only four observations, which accorded closely with those on the cat.

(53) Large dog. Ether for 6 hours. Left splanchnics cut. Blood-pressure steady at 110 mm.

Right ·71 gm. = ·81 mgm.
Left ·705 gm. = 1·35 mgm.

This illustrates the simple effect of ether anæsthesia, precisely as in the cat. To avoid this error, both splanchnics were next cut within the thorax, and faradisation applied to the nerve of one side or the other. Hardly a trace of exhaustion was produced.

(54) Small dog. Ether and chloroform. Both splanchnics cut within thorax. *Right* faradised for 3 hours, 3 minutes on and 2 minutes off, with occasional longer intervals for recovery. Blood-pressure generally rose from 100 to 160 or 170 mm.

Right ·50 gm. = ·67 mgm.
Left ·47 gm. = ·69 mgm.

(55) Medium sized dog. Ether. Both splanchnics cut within thorax. *Left* faradised for 3½ hours as above. Reaction of blood vessels good and sustained: even at end of experiment blood-pressure rose from 80 to 120 mm. (Cf. Fig. 7.)

Right ·8 gm. = 1·3 mgm.
Left ·66 gm. = 1·4 mgm.

(56) Small dog. Ether and chloroform. Both splanchnics cut within thorax. Left faradised *continuously* for 1½ hours. Blood-pressure reaction was fatigued sooner than the erection of hairs over the rump.

Right ·36 gm. = ·75 mgm.
Left ·36 gm. = ·65 mgm.

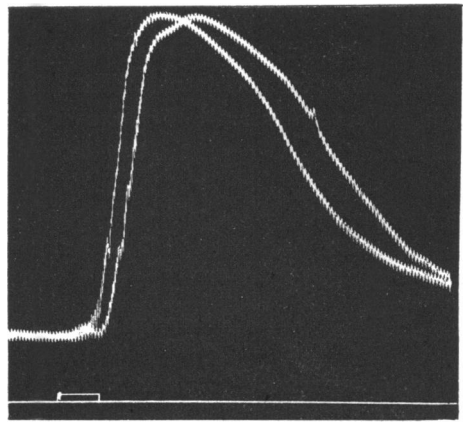

Fig. 7. From Exp. (55). Dog: both splanchnics cut, and left faradised for 3½ hours. Each gland yielded an extract of almost identical strength, A and B being 0·5 c.c. of each.

So slight is the change in the residual adrenalin caused by faradisation of the splanchnic nerves, that it would never have sufficed to convince me of the existence of the splanchnic control. But the experiments of Dreyer and of Tscheboksaroff, showing that adrenalin appears in increased quantity in the suprarenal venous blood when the splanchnics are stimulated, experiments that are of a delicate nature and that I have not attempted to repeat, do seem to prove that electrical excitation of the nerves causes excretion of adrenalin. This escape of adrenalin into the blood was illustrated by the investigators, whom I have quoted, by injection of the venous blood into a second animal and so proving its increased percentage of adrenalin.

But it can also be demonstrated by the reaction of the muscles of the same animal itself, either by those of the blood vessels or elsewhere. Asher's method proves it for the blood vessels, insomuch as excitation

of the splanchnics after removal of the abdominal viscera, that is of the muscles reacting directly to splanchnic stimulation, causes a rise of blood-pressure, but fails to do so when the suprarenals have also been removed. Several years earlier I had attempted identical experiments and with a like result, but did not regard them as sufficiently convincing for publication because the blood-pressure rise produced from the suprarenals, like that in Asher's series, was never as much as 20 mm. A rise of 15 mm. is too near to the limit of error. Since Asher's preliminary communication appeared[1], I have repeated the experiments and find his results to be definite and certain. In a pithed cat, a blood-pressure rise of 40 or 60 mm. can easily be obtained from the suprarenals. That is indubitable. My earlier failure was largely due to the fact that I had worked with ether anæsthesia, which reduces the difference to the low value given by Asher for rabbits. An example is:

(57) Small cat. 10.0 a.m. Pithed, brain and upper half of spinal cord being completely destroyed. Thorax opened, and both sympathetic trunks cut and placed on one shielded electrode.

10.15. Faradise both splanchnics, coil 17 cm. Blood-pressure rose from 48 to 166.

10.25. Remove intestines and kidneys. No loss of blood.

10.37. Stimulate splanchnics, coil 17 cm. Latent period of 13 seconds, and then rise from 36 to 84. No escape to body muscles, but rump hairs raised. (Cf. Fig. 8.)

10.43. Squeeze left suprarenal: no rise of blood-pressure.

10.45. Stimulate splanchnics again. Rise from 40 to 96.

10.48. Excise both suprarenals, taking care to preserve splanchnics.

10.55. Stimulate splanchnics, coil 17 and then at 0. Blood-pressure unchanged at 26, but rump hairs well raised.

11.15. Inject ·02 mgm. adrenalin. Blood-pressure rise similar to that at 10.45.

The observation was repeated in five different experiments, and was always entirely successful with pithed cats: a pressure rise of 66 mm. was the maximum, and 34 the minimum produced from the suprarenals, and there was always the same latent period[2].

Next I sought for evidence in the reaction of other muscles than those of the blood vessels. This is admirably provided by the denervated dilator pupillæ, because the iris and associated sympathetic muscular structures respond, after excision of the superior cervical ganglion, with greatly increased sensitiveness to minute quantities of

[1] *Zntrlb. f. Physiol.* XXIV. p. 928. 1910.

[2] Since the above was written, Prof. Asher has published the full account of his experiments in *Ztschr. f. Biol.* LVIII. p. 274. 1912. No tracings are reproduced. The blood-pressure figures certainly do show the effect of the suprarenal excretion, though as a matter of fact none are higher than the low figures which I had obtained in my own earlier experiments and thought to be inconclusive.

adrenalin. Such enhanced reaction is best seen a week or so after the ganglion has been excised. Then, peripheral stimulation of the cut splanchnics within the thorax, the cat being under ether and its blood-pressure recorded from the femoral artery so as to avoid inequality of circulation through either orbit, leads to the following results. For eight or nine seconds after the onset of the stimulation, as measured by the beginning of the blood-pressure rise, the eyes look alike, for ether anæsthesia generally induces a lobbing forward of the nictitating membrane on the sound side like that over the paralysed eye. Then suddenly the nictitating flashes back, the pupil dilates till the iris is a mere rim to the great, black globe, and the palpebral aperture is driven widely open. The normal eye remains unchanged.

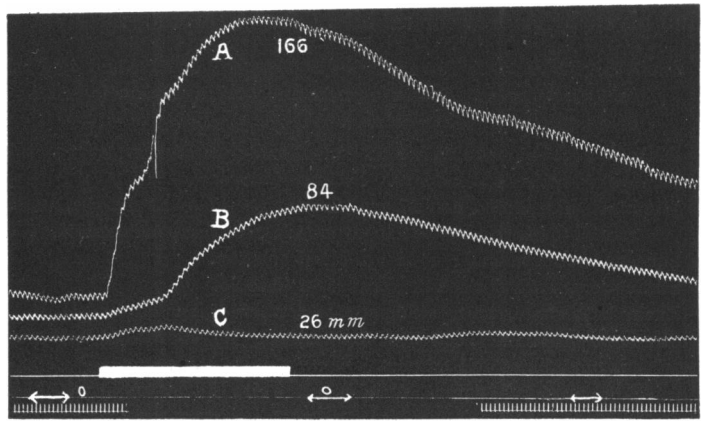

Fig. 8. From Exp. (57). Pithed cat. (A) Stim. both cut splanchnics, rise of 118 mm. (B) Ditto, after removal of abdominal viscera, rise of 48 mm., with longer latent period of 13 seconds. (C) Ditto, after removal of suprarenals; no rise, bl.-pr. 26. Drum was turned back between each, and stimulus always thrown in at the same time on the curve. Seconds marked below.

All these phenomena of sympathetic excitation persist for some time after cessation of the stimulus and fall of blood-pressure, and they are identical in character and time relations with those following intravenous injection of a small amount of adrenalin. Next, in the same cat, the suprarenals are quickly excised, either by a lumbar extraperitoneal incision or through the abdomen, and the splanchnics are again excited. The blood-pressure rises as high as before, but the denervated eye is almost irresponsive. The eyelids do not move at all, though the pupil dilates slightly and the nictitating is withdrawn

slowly and with more delay, the reaction soon vanishing with repetition. The contrast between the results before and after excision of the suprarenals is very great. It may be that the second effect, slight though it be, is similarly due to adrenalin, liberated from other paraganglia or from the actual processes of nervous excitation; or it may be from other metabolites. That the first and chief reaction is caused by suprarenal excretion seems to be beyond doubt.

The prettiest form of the experiment is that in which the suprarenal is excised only on one side: then faradisation within the thorax of the contralateral splanchnic causes full dilation of the pupil, whereas the ipsilateral and glandless nerve can evoke no such reaction at a distance[1].

Other metabolites probably can cause a reaction from the denervated pupil. Asphyxia does not readily do it in the adult cat, and the great "paradoxical pupillo-dilation" that was also observed in the early stages of etherisation in two out of the three adult cats, on which I made these experiments, was probably to be ascribed to their struggling alarm and its attendant emotional excretion of adrenalin when the ether was forcibly administered. But in the kitten asphyxia has been shown to cause paradoxical pupillo-dilation. At the time when Anderson's[2] experiments on this question were published, I supposed that his results might be explained by an excretion of adrenalin. To test the hypothesis I excised the suprarenals from a kitten. Before the operation light anæsthesia had readily produced paradoxical pupillo-dilation: subsequently it failed to do so, though deep anæsthesia was still effective.

In an adult cat the right superior cervical ganglion was excised, and the eye of that side in the days following was seen to react with great sensitiveness, being paradoxically dilated even in the slight anger shown by the animal when a stranger approached its cage. The suprarenals were then both excised by the lumbar route. Twenty-four hours later, while the cat was still strong and its rectal temperature normal, it was made angry; but not a trace of paradoxical dilation resulted. Light asphyxia was equally without effect. When, however,

[1] Since this paper was sent to the press, I have read the note by Joseph and Meltzer, *Amer. Journ. Physiol.* xxix. *Physiol. Proc.* p. xxxiv. 1912, describing a similar experiment in the rabbit. Their argument was not completed by the removal of the suprarenals, but the American authors have anticipated me in providing this good illustration of the excretion of adrenalin. Judging from their description, the reaction is not so evident in the rabbit as in the cat.

[2] This *Journal*, xxx. p. 290. 1903.

the animal was deeply asphyxiated to death, a dilation of the right pupil was caused in the terminal spasms.

These experiments of 1904 were not published, because the results seemed to me then somewhat inconclusive. The paradoxical effect was certainly very much depressed by removal of the glands, but that I was inclined to attribute to the harmful shock of the operation and not to lack of adrenalin, because the reaction could be attained with deep asphyxia. Now fuller knowledge makes it clear that excretion from the suprarenal glands is the cause of nearly all the phenomena of paradoxical pupillo-dilation that have been studied by various workers. Still, these old experiments have interest in respect of the present discussion because they prove that the suprarenals are not in absolutely all cases responsible for such paradoxical effects, which may appear in deep asphyxia although the suprarenals have been removed.

Attention to the blood-pressure records in the course of these experiments led, to my surprise, to another observation of interest. A well-known characteristic of the pressure curve seen when the splanchnics are stimulated under good conditions in the cat, is that it rises rapidly for nine or ten seconds; then, without any check in the heart's rhythm, the curve is sharply cut down nearly to the level from which it came, whence it rises slowly again so long as the stimulus is continued. The cusp of the curve always is placed at the same time interval from the beginning of the rise, and the instant of the turn is that very moment when the nictitating membrane and other structures of the denervated eye first move. The drop is, paradoxically, due to the liberation of adrenalin into the blood. Further proof of this is given in the detailed experiments that follow:

(58) In an etherised cat, from which the superior cervical ganglion had been excised 8 days previously, both splanchnics were cut above the diaphragm. Their stimulation yielded the typical result, pressure rising from 140 to 164, a sharp drop to 120, and then a slow rise to 150. Exactly at the turning point from 164 the nictitating and iris reacted on the denervated side. Both suprarenals were then excised by opening the abdomen, the viscera being covered with hot, moist flannels. The abdomen was closed, and the splanchnics again stimulated. Pressure rose from 130 to 170, steadily and without any secondary drop: the nictitating moved back very slowly and the iris dilated just a little. Repetition gave always the same type of blood-pressure curve, an absolutely even rise that was uniformly upheld on a smooth plateau.

Next a small dose of adrenalin, ·005 mgm., was injected into the cat's jugular vein. A slow rise of blood-pressure resulted. The splanchnics were stimulated: a smooth rise again. Finally the same dose of adrenalin was injected into the jugular, and at the same moment the splanchnics were faradised. The curves of blood-pressure rise did not add up to a higher level, but a switchback curve of rise and fall and rise was produced, just like that seen with splanchnic excitation and intact suprarenals.

The success of these experiments depends upon the condition of the animal. Section of the vagi makes no difference to the result. In cats that have been admitted to the laboratory overnight and are still alarmed by their strange surroundings, a condition in which the suprarenals are always found to be somewhat exhausted of adrenalin (cf. p. 379), excitation of the splanchnics rarely produces a secondary fall in the blood-pressure: indeed, then, the pressure curve more often shows a slight secondary rise at the moment when adrenalin should be

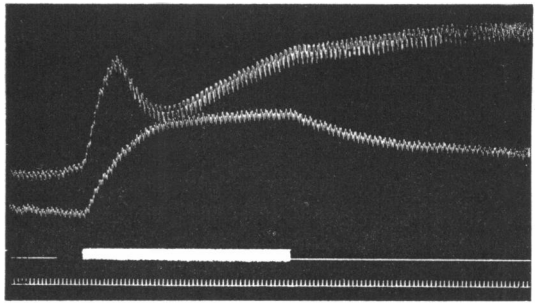

Fig. 9. Etherised cat. Upper curve, stimulation of both cut splanchnics within thorax: bl.-pr. 70–120–96–130. Suprarenals then excised and both splanchnics again stimulated: lower curve, 50–92 upheld.

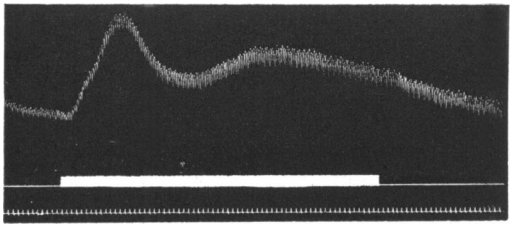

Fig. 10. From same Exp. as Fig. 9. After excision of the suprarenals, the splanchnics were again stimulated and adrenalin was at the same time injected into the jugular vein. The curve closely resembles the upper one in Fig. 9 before excision of the glands.

entering the circulation. Best results are obtained with animals that purr when stroked, and generally manifest a sense of *bien être*. In such (cf. Exp. 59), a clear drop is always seen with splanchnic stimulation, and is often caused too by the simple injection of a minute quantity of adrenalin itself, when the pressure is standing fairly high. From a very low pressure, as in a pithed animal, the splanchnics cause no drop at all but simply a big rise (cf. Fig. 8). Therefore, that the

comparison may be just, the blood-pressure after removal of the suprarenals should be at much the same level as it was before. The fairest way to show the contrast is by removing the gland on one side alone, and so comparing the blood-pressure curve from the glandless splanchnic with that from the intact nerve when both are playing on the viscera under conditions that are precisely alike for each.

(59) Large cat, in good condition; in stock 6 days.
9.30. Ether. Cut vagi.
9.45. Cut both sympathetic trunks within thorax, and clamp each separately for excitation. Artificial respiration.
10.0. Stimulate right and left splanchnics successively. Each gave precisely the same curve of rise and fall and rise.
10.15. Excise left suprarenal extraperitoneally by lumbar incision.
10.20. Stim. right spl.: bl.-pr. 106–150–104–140.
10.40. Stim. left (glandless) spl.: bl.-pr. 90–130, upheld.
11.20. Stim. left, 90–130–124.
11.28. Stim. right, 90–122–88–124. } (Cf. Fig. 11.)
11.52. Inject ·005 mgm. adrenalin into jugular vein, 90–100–74.
12.0. Repeat left and right spl. stim. with same contrasted results.
12.15. Cut and stim. left cardiac accelerators: only slight rise of bl.-pr.
12.20. Cannula placed in central end of ligatured left subclavian artery, so as to inject solution into aorta beyond the arch and the heart. Adrenalin, ·005 mgm., bl.-pr. 76–88–64–94.
12.24. Stim. right spl.: bl.-pr. 90–152–114–130.
12.28. Stim. left spl.: 90–132, upheld.
12.31. Stim. left, and 8 seconds after commencement of stimulus inject ·005 mgm. adrenalin into subclavian artery: bl.-pr. 90–106–92–110. (Cf. Fig. 12.)
12.55. Open abdomen laterally, so as to avoid exposure of viscera, dissect out entire mass of postganglionic mesenteric nerves to stomach and intestines, and stim: pure rise 84–140.
1.10. Cut mesenteric nerves, and stim. peripherally: pure rise 70–96, and upheld.
1.15. Stim. mesenteric nerves, and inject ·005 mgm. adrenalin into subclavian artery: bl.-pr. 70–100–76.

In each case, whether injected artificially into the jugular vein, or liberated from the glands by the abnormal and artificial excitation of all the splanchnic fibres simultaneously, the adrenalin passes through lungs and heart before it reaches the intestinal blood vessels. That partly explains the long latent period of 8 to 12 seconds before the adrenalin effect becomes manifest. But the fall is not due to altered action of the heart, for it is equally seen when adrenalin is injected into the aorta beyond the heart. It is apparently caused by the action of adrenalin on the very muscles which are at that moment contracting in response to the splanchnic nervous impulses.

Dale's[1] analysis with ergotoxine added weight to the opinion that

[1] This *Journal*, xxxiv. p. 163. 1906.

the secondary fall indicates a stimulation of vaso-dilator fibres coincidently with, and at last prepotently over, the vaso-constrictors. That may be so, or not. For the present argument it is enough to recognise that this well-known drop in the curve, when the splanchnics are stimulated, is caused by the discharge into the blood of suprarenal secretion. How the drop is caused, whether it be a matter of vaso-motor balance, or the signal of a more subtle play between adrenalin and nervous excitation, that is a question lying beyond.

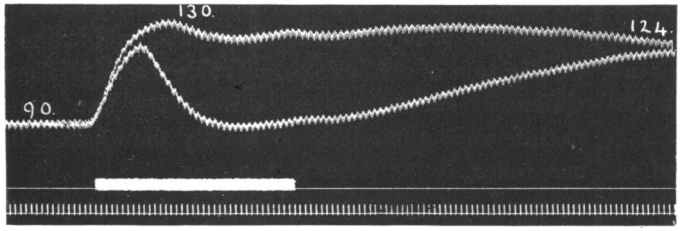

Fig. 11. From Exp. (59). Etherised cat. Both splanchnics cut within thorax. Left suprarenal excised. Upper curve, stim. left (glandless) splanchnic: bl.-pr. 90–130–124. Lower curve, stim. right splanchnic: bl.-pr. 90–122–88–124. Time marked in seconds.

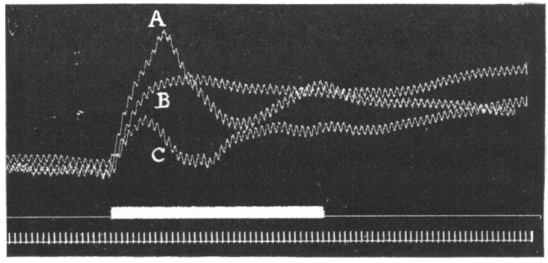

Fig. 12. From Exp. (59). (A) Stim. right spl. 90–152–114–130. (B) Stim. left (glandless) splanchnic, 90–132. (C) Stim. left splanchnic, and inject ·005 mgm. adrenalin into subclavian artery; bl.-pr. 90–106–92–110.

Various explanations might serve for the anomaly that prolonged electrical excitation of the splanchnics fails to cause exhaustion of residual adrenalin to anything like the same degree which is attained in the reflexes from the central nervous system.

The glandular nerves certainly do react to the artificial stimulus of faradisation, but it may be that they soon become irresponsive. Or the nerves stimulated may be only excretory, and so fail of action when no more material lies within their immediate grasp, whereas in the nervous

reflexes the whole machinery is used to feed the excreting nerves. Or again, it may be urged that the nerves contain anabolic as well as excretory fibres, and that both are excited together when the trunk is directly faradised. Opposed to the last view are the following considerations:

(*a*) Days after section of the splanchnics on one side, no difference is found in the adrenalin content of the two glands, when the cat is resting quietly. Anabolism seems to proceed without central control, and both are fully loaded. The decentralised gland in all experiments was found to contain as much or more adrenalin than its fellow.

(*b*) It is improbable that coarse faradisation should strike so even a balance in the excitation of anabolic side by side with excretory fibres, that but little difference should appear between the two glands, and that yet a great difference should be so readily manifested in every prolonged nervous reflex.

(*c*) Stimulation of one splanchnic does not cause any difference between the cortical cells of the two glands.

The question remains undecided. Adrenalin does escape from the suprarenals into the blood stream, and that escape is controlled by the splanchnic nerves.

THE REFLEX NATURE OF THE SPLANCHNIC CONTROL.

Electrical excitation of various afferent nerves will induce reflex exhaustion of residual adrenalin very rapidly, and that too though the reflex is not necessarily one associated with high rise of blood-pressure.

(60) Ether. Left splanchnics cut within thorax. Left sciatic nerve faradised at intervals for 4 hours. Blood-pressure rise only 20 mm.

Right ·47 gm. = ·04 mgm.
Left ·45 gm. = ·34 mgm.

Such exhaustion developed sooner than would have been the case with ether anæsthesia alone. The reflex occurred at a level at least as high as the vaso-motor centre in the medulla oblongata, for it was never obtained when the spinal cord was transected at a plane above the origin of the splanchnic efferent nerves[1].

[1] This failure of the suprarenal reflex agrees with Sherrington's observation of the difficulty of exciting any ordinary vaso-motor reflexes from the spinal cord. (This *Journal*, XXXVIII. p. 380. 1909.)

(61) Ether. Spinal cord transected at the first thoracic segment. Left splanchnics cut within thorax. Sciatic and other afferent nerves stimulated in succession for 1 hour. Good reflexes of the body muscles: blood-pressure only 40 mm. and practically no rise with reflexes.

Right ·17 gm. = ·19 mgm.
Left ·18 gm. = ·19 mgm.

(62) Decapitated, and cord severed at second cervical. Left splanchnics cut within thorax. Various afferent nerves faradised for 1 hour: brisk bodily reflexes, but blood-pressure rose only 20 mm.

Right ·29 gm. = ·15 mgm.
Left ·27 gm. = ·12 mgm.

In the same way, it was found that, after pithing the brain, transection of the spinal cord at the first thoracic segment prevented the usual exhaustion by the splanchnic nerves. The experiments with β-i prove that low blood-pressure in itself does not check the nervous exhaustion.

The level of the mechanism controlling the suprarenals, at which this afferent reflex occurs, is not higher than the corpora quadrigemina.

(63) Ether. Skull trephined, and cerebral hemispheres removed entirely after transection just above the anterior corpora quadrigemina. Ether then stopped: left splanchnics cut within thorax. Spontaneous respiration, and lively reflexes. Blood-pressure 150. For next 2 hours the central ends of the sciatic and other afferent nerves were faradised, so as to produce strong skeletal muscle reflexes, and blood-pressure rise of 60 or 70 mm. each time.

Right ·27 gm. = ·01 mgm.
Left ·26 gm. = ·15 mgm.

The cat had been in stock 4 days: both glands were partly exhausted by the first $\frac{3}{4}$ hour dissection of the brain, and then exhaustion of the right gland was completed in the next two hours' reflex stimulation after the left nerves had been cut.

Apparently the reflex control of the suprarenals is associated with the nervous machinery in the neighbourhood of the vaso-motor centre which governs other sympathetic emotional musculature.

Hæmorrhage. A few experiments were made upon the immediate effects of copious hæmorrhage, to see whether under such conditions an increased drain upon the suprarenals would be associated with the vaso-motor reflexes. When an etherised cat is bled 30 c.c. or more, the blood-pressure falls abruptly: in a few minutes it is picked up again by a strong vaso-constrictor action. Repetition of the hæmorrhage reduces the blood-pressure to a low level, and the animal's brain becomes very torpid so that hardly any anæsthetic is needed to maintain complete quietude. The bodily reflexes are lessened, but, of course, not

extinguished; and the same holds true for the vaso-motor reflexes. Exhaustion of residual adrenalin was evidenced in the usual way by section of the splanchnics; but it did not appear to be much greater than would be caused under ether anæsthesia and the ordinary conditions of experiment.

Remarks.

A broad review of the facts put forward in this paper sees their agreement with those of other workers in proving that there is a very sensitive and prompt control by the nerves of adrenalin excretion from the suprarenal glands. Adrenalin has justly been included in the catalogue of the hormones, but, in default of fuller knowledge, such classification rather tended to suggest that its secretion and consumption would proceed steadily and inevitably as one of the chemical adjustments of the body that are transacted automatically below the level of nervous control. This idea was not explicitly laid down in Starling's general view of the hormones, and it is most emphatically not true in respect of adrenalin. The vertebrate animal controls a widely distributed field of plain muscle directly through the sympathetic efferent nerves. Intimately connected with these efferent nerves are the paraganglion cells of the suprarenal, secreting the hormone, adrenalin, which can evoke a response from the peripheral muscles identical with that to the nervous impulse. In the various reflex actions of the vaso-motor centre the gland cells also are involved. The efferent path from the bulbar centre to the muscles is twofold—directly by nervous impulses to the muscles, and indirectly by nervous impulses to the suprarenals, whence the chemical messenger, adrenalin, is despatched to the same muscles almost contemporaneously with the nervous impulses. The nature of this double action has never yet been analysed, though it may contain the essential secret of nervous activity. Very suggestive are two features of the interaction; firstly, that the response of a muscle to adrenalin is quickest when the muscle is one that is being incessantly played on by the direct nervous reflexes of daily life[1]; and secondly, that removal of the suprarenals leads to atony and nervous paralysis in those muscles which have actually been made use of in nervous reflexes by the animal after loss of the glands[2]. It is my hope to bring forward experiments dealing with this question in a later paper.

[1] This *Journal*, xxxii. p. 426. 1905.

[2] *Ibid.* xxxi. *Proc. Physiol. Soc.* p. 20. 1904.

SUMMARY.

By measurement of the amount of adrenalin that can be extracted from the suprarenal glands of the cat, it is proved that:—

(1) The suprarenal glands contain almost exactly equal amounts of adrenalin on each side.

(2) The fright induced by morphia or β-tetrahydronaphthylamine exhausts the residual adrenalin.

(3) All ordinary conditions of anæsthesia, with ether, or chloroform, or urethane, are attended by exhaustion of adrenalin.

(4) Excitation of afferent nerves, such as the great sciatic, or direct injury to the brain, whether by simple pithing or by faradisation, also causes loss of adrenalin.

(5) The centre controlling such loss is close to the bulbar vaso-motor centres.

(6) The efferent path is by the splanchnic sympathetic nerves. Their section prevents this exhaustion; and ether, chloroform, and other drugs, such as pilocarpine and physostigmine, or even diphtheria toxin, appear to have no exhausting action directly on the suprarenals[1].

(7) Faradisation of the splanchnic nerves discharges adrenalin into the blood, causing a characteristic drop in the rising curve of blood-pressure, and such phenomena as paradoxical pupillo-dilation.

From the variety of methods and the rapidity with which such adrenalin loss can be induced through the splanchnic nerves, it appears probable that the suprarenal glands are played upon by the splanchnic nerves in the emotional and vaso-motor reflexes with almost as delicate and everchanging an adjustment as are the muscles of the peripheral tissues connected with the sympathetic nerves.

[1] Ultimately, however, the glands must be capable of automatic excretion, for the decentralised gland suffices to keep the animal alive. If in a cat the suprarenal on one side be removed, and the splanchnic nerve of the other divided, the cat does not die until the second suprarenal has also been excised.

This work was carried out in the tenure of a Beit Memorial Fellowship. A grant toward its expenses had previously been received from the Royal Society.