

## OBSERVATIONS ON THE PHYSIOLOGICAL ACTION OF EXTRACTS OF THE SUPRA-RENAL BODIES.

BY J. N. LANGLEY, Sc.D., F.R.S., *Deputy Professor of  
Physiology in the University of Cambridge.* (One Figure in Text.)

IN the course of an investigation upon the action of various poisons upon nerve-cells I had occasion to inject supra-renal extract. The results seemed to me to make it desirable to inquire more nearly into the mode of action of the extract. In the following pages I give an account of the inquiry, although the conclusion on the main point is still provisional.

My observations, unless otherwise mentioned, were made upon cats. The animals were in all cases anæsthetized, first with chloroform or ether and then with A.C.E. mixture. After a few preliminary trials, boiled extracts after the manner of Oliver and Schäfer were made. The supra-renal bodies were taken a short time after death<sup>1</sup> and dried in a desiccator, the glands of each animal being kept separate. When required for use a portion of the dried substance was ground with sand, and then with .75 p.c. salt solution, a drop of acetic acid added and the mixture boiled and filtered. The proportion of dried gland to salt solution was in all cases 1:100, *i.e.* a 1 p.c. extract of dried gland was used. Dogs' supra-renal bodies were employed in nearly all cases; a few experiments with those of the cat gave no difference in result.

Having obtained the effects described in this Paper with the 1 p.c. extracts of dried glands, the experiments were repeated with Burroughs and Wellcome's supra-renal tabloids and similar effects obtained. As a rule an extract of one tabloid in six c.c. of salt solution was used, this corresponds to about 1.1 to 1.3 p.c. extract of the dried gland. I shall refer to this extract as (T. 1 in 6). Occasionally stronger solutions were employed, *viz.* one tabloid to three c.c., and one tabloid to one c.c. of salt solution. The solutions were prepared in the manner given for the dried glands, except that they were not ground with sand. I quote as

<sup>1</sup> If the glands are kept moist after death, a considerable destruction of the active principle appears to take place.

a rule the experiments made with these solutions since they vary less in strength than the extracts of the dried supra-renals of different animals.

*Secretion of Saliva.* Oliver and Schäfer<sup>1</sup>, who were the first to study effectively the physiological action of supra-renal extracts, are so far as I know the only authors who have made direct observations with regard to its influence upon the secretion of saliva. They obtained only negative results.

I find that the extract causes a lively secretion from all the salivary glands, and some secretion from the buccal, œsophageal and tracheal mucous membranes. On the sub-maxillary gland I have made a considerable number of experiments, on the sub-lingual and parotid one or two only.

The rate and duration of the secretion increase, other things being equal, with the amount of the extract. Thus with amounts up to 10 c.c. of a 1 p.c. extract, the flow of saliva may last for a period varying from half a minute to nine minutes, the duration depending in part upon the rate of injection.

On injecting doses of 5 c.c. each at intervals of a quarter of an hour, the duration of the secretion is much the same with each, and the amount of saliva obtained is sometimes undiminished (cp. Exp. V.) but sometimes decreases. If a fresh injection is made just before the secretion caused by the first has stopped, the amount of saliva obtained and the duration of the flow are, so far as my few experiments on the point go, less with the second than with the first injection, nevertheless protracted secretion may be obtained by repeated injections.

A small dose of supra-renal extract, though sufficient to cause a great rise of blood-pressure, may have no secretory action. When 3 to 5 c.c. of the extract (T. 1 in 3, to T. 1 in 6) are injected in a quarter to half a minute, the secretion begins in 10 to 30 seconds from the beginning of the injection. It is later than the rise of blood-pressure, dilation of the pupil and most of the other effects. The flow rapidly reaches a maximum and rapidly declines. The following experiment will serve to show the course of events.

EXP. I. Submaxillary duct connected with a tube graduated in millimetres, 10 mm. containing 0.071 c.c. Chorda-lingual and cervical sympathetic nerves tied and cut. The rise of saliva in mm. each 15 secs. was read off.

The rate of secretion on stimulating the secretory nerves was first taken. It was

|                   |   |   |   |    |    |   |   |   |   |   |   |   |   |                   |
|-------------------|---|---|---|----|----|---|---|---|---|---|---|---|---|-------------------|
| 33                | 8 | 5 | 4 | 20 | 10 | 3 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 0                 |
| Ch <sup>(1)</sup> |   |   |   |    |    |   |   |   |   |   |   |   |   | Sy <sup>(2)</sup> |

<sup>(1)</sup> Chorda tympani stimulated.

<sup>(2)</sup> Sympathetic stimulated.

<sup>1</sup> This *Journal*, xviii. p. 230. 1895.



That the supra-renal extract stimulates some peripheral structure is shown by the fact that it causes secretion, in little if at all diminished quantity, after injection of a large dose of nicotine.

In the cat 5 mgrms. or less of atropin sulphate paralyses the chorda tympani. I was therefore somewhat surprised to find that after 10 mgrms. of atropin<sup>1</sup> had been given, 5 c.c. of the supra-renal extract might give rise to a fairly free secretion, as in the following experiment :

Exp. III. 5 c.c. of supra-renal extract (T. 1 to 6) caused a secretion, lasting  $4\frac{1}{2}$  minutes. 10 mgrms. of atropin were then injected. 8 minutes later 5 c.c. of the extract still caused a secretion, but only about half the amount caused by the first injection, and it lasted only  $2\frac{3}{4}$  minutes. In other experiments in which the cat was smaller than in this case, the same amount of atropin caused a much greater decrease in the secretory effect of supra-renal extract (cp. Exp. IV.).

The secretion, however, although sometimes considerable, as in Exp. III., was less than normal, and in some experiments was but slight (cp. Exps. IV. V.). Further, it appeared that if a large dose of atropin was given, as 30 mgrms., 5 c.c. of supra-renal extract had then no effect. The effects obviously depended upon the relative amounts of the two substances present in the blood; very much as in the case of atropin and pilocarpin, which I described a good many years ago<sup>2</sup>. The resemblance extends to some other points. When pilocarpin causes a secretion after the chorda tympani has been paralysed by atropin, it at the same time renders the chorda tympani to some extent effective; as the secretion decreases, the chorda causes less and less secretion, and shortly after the secretion has ceased, the nerve returns to its paralysed state. A similar temporary return of effectiveness to the chorda tympani occurs on injecting supra-renal extract after atropin (cp. Exp. IV.). There are one or two minor differences to note. In order to give sufficient pilocarpin to paralyse 10 mgrms. of atropin injected into the blood, it must usually be injected into the duct or into the artery of the gland, for if it be injected into the blood, the animal will probably be killed by it before enough has been given to antagonise the atropin. This is not the case with supra-renal extract. The difference is to be explained partly by the supra-renal extract being a much more powerful antagonist of atropin than is pilocarpin, and partly by the difference in their action on the heart and blood

<sup>1</sup> Atropin is used throughout for atropin sulphate.

<sup>2</sup> *Journ. of Anat. and Physiol.* xi. p. 179. 1876. *This Journal*, i. p. 358. 1878; iii. p. 11. 1880.



Exp. V. Right sup. cer. ganglion excised under ether. Ten days later, chloroform and A. C. E. given. Right sub-max. duct connected with graduated tube, 10 c.c. = 0.033 c.c. Chorda-lingual n. tied and cut. Flow of saliva taken each 15 secs.

11.56. Saliva flow.  $\frac{17.47.43.10.5.3.2.1}{2} \cdot \frac{1}{2} \cdot \frac{1}{2} \cdot 0$

Ch

12.8. 5 c.c. of supra-renal extract (T. 1 in 6) injected into femoral vein in 25 seconds. The secretion begins just before the end of the injection. Total secretion 156½ mm.

12.25. Saliva flow.  $\odot^{(1)} \cdot \ominus^{(1)} \cdot 18 \cdot 18 \cdot 17 \cdot 20 \cdot 23 \cdot 20 \cdot 14 \cdot 8 \cdot 4 \cdot 1 \cdot 1 \cdot \frac{1}{2} \cdot 0 = 153\frac{1}{2}$  mm.  
<sup>(1)</sup> 5 c.c. of supra-renal extract injected in 35 seconds

12.49. Inject 5 c.c. supra-renal extract. Total secretion 154 mm.

1.5. " " " " " " 163½ mm.

1.21. " " " " " " 151 mm.

2.23. Inject 10 mgrms. of atropin sulphate. Two injections of extract at 2.29 and 2.36 each of 5 c.c., caused only a slight secretion. At 2.49, 10 c.c. of extract caused a flow of 78 m.m.

Supra-renal extract causes also secretion from the sub-maxillary gland of the rabbit and the dog. In the dog, the flow has seemed to me to be relatively less than in the cat.

The effect of the extract on the blood vessels of the gland I shall take under the heading of Blood Vessels.

*Lachrymal gland.* Supra-renal extract causes a free secretion from the lachrymal glands: it produces a secretion though a diminished one after intravenous injection of 5 to 10 mgrms. of atropin. In one case in which the secretion on the two sides was compared, the superior cervical ganglion being excised on one side, and intact on the other, the secretion was more abundant on the excision side, but the difference observed may have been accidental.

In the rabbit, there does not appear to be any special secretion from the Harderian gland on injection of the supra-renal extract, though some fat globules from the Harderian gland may be found in the fluid flooding the eye.

*Sweat glands.* I have not found any trace of secretion of sweat on injecting supra-renal extract intravenously, although a secretion was obtained on similarly injecting nicotine. Nor have I found any, on injecting the extract (T. 1 in 3 and T. 1 in 1) sub-cutaneously into the pad of the foot, although it was readily obtained by similar injection of 0.1 p.c. pilocarpin nitrate. In one experiment with the stronger extract (T. 1 in 1) there was after some time the merest trace of secretion, but this may have been spontaneous and caused by warming the foot.

*The secretion of bile. The gall bladder.* If a cannula be tied in the common bile duct in the cat, and the connection with the gall bladder be clamped, injection of supra-renal extract causes an increase in the rate of flow of bile, reaching a maximum in two to four minutes, and then slowly declining below the previous rate: the decrease may pass on to a temporary cessation of the flow; occasionally there is a temporary decrease in rate of flow before the increase, but this may be due to the shallower breathing, caused for a time by the extract.

EXP. VI. The bile duct was connected with a graduated tube, of which 10 mm. contained 0.033 c.c. The flow in millimetres was taken each minute.

(i) 4. 6<sup>(1)</sup>. 8. 6. 6. 3. 3. 1½.

(ii) 2. 2. 2½<sup>(1)</sup>. 4. 5. 4. 2½.

<sup>(1)</sup> Inject 5 c.c. supra-renal extract (T. 1 in 6).

When the duct from the gall bladder is not clamped, there is usually a preliminary slowing of the flow of bile. The slowing is probably due to inhibition of the tone of the gall bladder, so that the secretion passes into this instead of into the cannula.

EXP. VII. Arrangement as in the previous experiment, but the duct of the gall bladder was not clamped.

(i) 4. 4. 2<sup>(1)</sup>. 0. 0. 7. 9. 8. 6. 5. 3.

(ii) 2. 2. 1<sup>(1)</sup>. 0. 2. 7. 7. 5. 5. 3½. 3. 2½. 2½.

<sup>(1)</sup> Inject into jugular 5 c.c. supra-renal extract (T. 1 in 6).

Sometimes, and especially if the pressure in the tube is a little raised, the injection causes a fall of pressure of varying duration, the fluid passing back into the gall bladder.

EXP. VIII. Arrangement as in previous experiment. 10 mm. of tube=0.048 c.c.

(i) 2½. 2. 2. 3. 3. 5<sup>(1)</sup>. -6. -1. 5. 3. -1. -2. -4. -4. -5. 3<sup>(2)</sup>. 0. 12<sup>(2)</sup>. -2. 1. -3. -2. -2. 0. 0. 1. ½. 2½.

<sup>(1)</sup> Inject into femoral vein 5 c.c. of supra-renal extract.

<sup>(2)</sup> The flow of bile during this minute was probably caused by the much deeper breathing which occurred.

In an experiment in which the upper part of the duodenum was cut open, no flow of bile into the intestine followed injection of supra-renal extract, but at the end of an experiment a good deal of bile was commonly found in the intestine.

*Pancreatic Secretion.* In the cats on which I experimented, the pancreatic secretion ceased very soon after the insertion of the cannula, in no case was any secretion caused by intravenous injection of supra-renal extract. It should be mentioned, however, that injection of

0.4 p.c. HCl into the duodenum also caused no secretion. In the dog, the effects varied; when the spontaneous secretion was very slight, supra-renal extract (5 to 10 c.c. of T. 1 in 6) had a very slight effect, causing a trivial increase of the secretion for two or three minutes after the injection; when the spontaneous secretion was moderately fast, the effect of the injection sometimes led to a considerable increase in the secretion, beginning 20 to 30 seconds after the beginning of the injection.

*The eye.* Lewandowsky<sup>1</sup> noticed that supra-renal extract causes in the cat dilation of the pupil, withdrawal of the nictitating membrane, separation of the eyelids, and protrusion of the eyeball. Boruttau<sup>2</sup> confirmed the occurrence of pupil dilation.

The effects, as mentioned by Lewandowsky, are very obvious in the cat; less obvious in the rabbit, although in this animal also, the dilation of the pupil is easily seen. The stimulating action of a sub-maximal dose of the extract is greater on the pupil than on the nictitating membrane, and greater on the latter than on the eyelids; the difference may be shown by a difference in the time of beginning of the several movements.

Lewandowsky also showed that supra-renal extract was still effective after the superior cervical ganglion had been excised, and the nerve-fibres proceeding from it allowed to degenerate. He inferred that the extract must stimulate directly the muscle substance and not do so by way of the nerve-endings. I have confirmed this observation of Lewandowsky; notwithstanding that after degeneration of the post-ganglionic fibres of the superior cervical ganglion, the eye, in deeply anæsthetized cats, is in a state similar to that produced by stimulation of the cervical sympathetic (Kowalevsky, Langendorff); supra-renal extracts still further dilate the already nearly maximal pupil, cause the very slightly projecting nictitating membrane to be completely withdrawn, and lead to still wider separation of the eyelids.

Lewandowsky's view that the various eye effects are produced by a direct action of supra-renal extract on the unstriated muscle is I think correct, but it must be borne in mind that effects of the same kind are also produced by a decrease of the impulses passing by the 3rd nerve. In the cat, in life, after excision of the superior cervical ganglion, the nictitating membrane may project over nearly half of the cornea, or be almost completely hidden; and the aperture of the eye-

<sup>1</sup> *Arch. f. (Anat. u.) Physiol.* 1899. p. 360.

<sup>2</sup> *Arch. f. d. ges. Physiol.* LXXVIII. p. 112. 1899.



lids varies considerably. These variations it is not unlikely are due to variations in the degree of protrusion of the eyeball, but the fact that they occur makes it necessary to use some caution in interpreting the movements of these structures. Nevertheless I adopt Lewandowsky's view of a direct action of the supra-renal extract on the unstriated muscle, partly because the effects produced by the extract after degeneration of the post-ganglionic fibres seem to me to be too great to be accounted for by a decrease of the impulses travelling down the 3rd nerve, and partly because I have not found that cutting the 3rd nerve intra-cranially, or ligaturing the short ciliary nerves peripherally of the ciliary ganglion—the optic nerve being ligatured with the ciliary nerves—makes any essential difference to the normal exciting action of supra-renal extract.

The stimulating effects as noticed by Lewandowsky are brief, especially on the pupil. I have not been able to satisfy myself that there is any stimulating, or other action on the unstriated muscle of the sphincter of the pupil.

It will be noticed that the tissues stimulated are only those which are governed by sympathetic nerves, the tissues governed by the 3rd nerve, so far as the evidence goes, are unaffected.

In the dog I have made a few experiments only. The animals weighed 6 to 8 kilos. Up to 10 c.c. of extract (T. 1 in 6) the eyelids and the nictitating membrane were little if at all affected and the pupils slowly and somewhat feebly contract instead of dilating. Large doses (10 to 25 c.c. of T. 1 in 3) killed the animal by stopping the heart, whether the vagi were cut or intact; there appeared however to be slight dilation of pupil and other usual eye effects, independently of the cessation of heart-beat.

I have not found any paralysing influence on the cervical sympathetic after giving 32 c.c. of the 1 p.c. extract in several doses during 28 minutes, or by giving 10 c.c. of a 2 p.c. solution in two doses in 10 minutes.

*The heart and blood vessels.* It has been shown by Gourfein<sup>1</sup> and by Cybulski<sup>2</sup> that supra-renal extract in sufficient dose paralyses the vagus. The statement is easily confirmed. The paralysis is brief. In the cat, 5 to 10 c.c. of 1 p.c. extract cause as a rule paralysis for 30 seconds to 1 to 2 minutes, but there is considerable difference in

<sup>1</sup> Gourfein, *C. R. Acad. des Sci.*, 5 Aug. 1895.

<sup>2</sup> Cp. Szymonowicz, *Arch. f. d. ges. Physiol.* LXIV. p. 146. 1896.

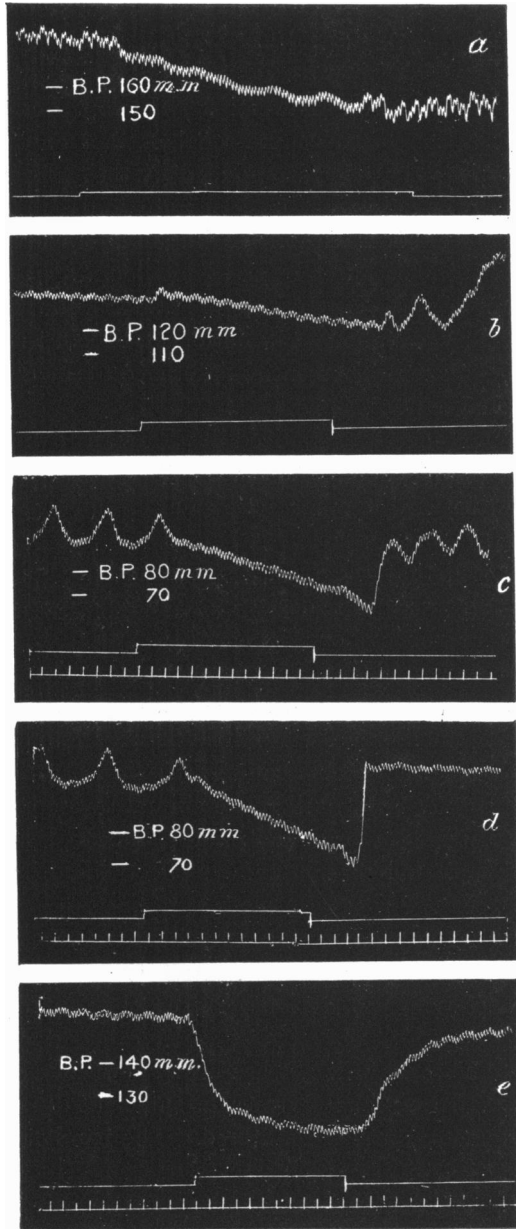


Fig. 1. Cat. Effects of stimulating the peripheral end of the vagus after injection of supra-renal extract, *a* is taken from one experiment, *b*—*d* from another.

different cases, and the paralysing effect may be less with repeated injections.

Curious curves are obtained when a dose is given a little short of that required to make stimulation of the peripheral end of the vagus entirely ineffective on the tracing.—The respiratory curves disappear or are much lessened, and there is slow gradual fall of blood-pressure, with a trifling decrease in heart rate; or the fall may be sudden, though the rate of heart-beat is not greatly decreased. Some of the varieties of tracings are shown in Fig. 1.

The curves at first sight suggest some vaso-dilator action, lowering the blood-pressure, but they are probably due to weakening of the heart-beat without much variation in rate. In this case, the lessening of the respiratory curve must be due to an equalising of the strength of the heart-beat; *i.e.* the normal respiratory curves must be largely due to a rhythmic variation in the strength of the heart-beat.

According to Oliver and Schäfer (*op. cit.*), injection of the supra-renal extract in the dog after section of both vagi causes no slowing of the heart-beat, but only quickening. In the cat I find that after section of the vagi, supra-renal extract sometimes causes quickening only of the heart-beat, but that not infrequently the rate is irregular during the rise of blood-pressure, some slow beats occurring; in one case the heart stopped for three minutes. The slowing, when it occurs, is I think due to the increased work thrown on the heart; whether the action is entirely direct on the heart-muscle or is partly due to a post-ganglionic axon-reflex there is hardly sufficient evidence to show, but the slow beats caused by the extract are fewer or absent after injection of nicotine, although the rise of blood-pressure is commonly greater.

*Blood vessels of the sub-maxillary gland.* The primary effect of supra-renal extract on the vessels of the gland is constriction and not dilation. The gland becomes pale soon after the injection, and remains so for 30 seconds or more, it very gradually loses its pale tint, and at the maximal rate of secretion it is distinctly redder than at starting, and the flushing only gradually disappears, lasting longer than the secretion. The pallor is not so great as that produced by stimulating the cervical sympathetic, nor is the flushing so great as that produced by stimulating the chorda tympani. Both of these nerves have much their usual action on the blood flow, if stimulated whilst the secretion is going on.

In the experiment mentioned above (p. 242) in connection with the secretion of saliva, with regard to the effect of degeneration of the

post-ganglionic sympathetic nerve-fibres, I paid attention to the colour of the gland during the injection of supra-renal extract. There was slight but distinct primary pallor of the gland lasting a minute or more, and later a gradual slight flushing. The effects were in fact the same as those produced normally, though they were rather less distinct. The flushing on stimulating the chorda tympani was also rather less than normal. The result seems to me to show that the blood vessels of the sub-maxillary gland are directly affected by supra-renal extract.

The view that supra-renal extract acts directly on the unstriated muscle of the blood vessels was first put forward by Oliver and Schäfer; they showed that the extract stimulated some peripheral structure, and as they found that it had a veratrin-like action on striated muscle, they concluded that it acted also directly on unstriated muscle.

*Action on other blood vessels.* It was noticed by Spina<sup>1</sup> that the injection of supra-renal extract caused some reddening and increase of size of the brain during the general rise of arterial blood-pressure, so that in this case the peripheral vessels were not constricted.

The extract has in fact a very unequal action on the blood vessels of different parts of the body, and its action in general runs parallel with the action of the sympathetic nerves on the blood vessels. Thus injection of supra-renal extract causes great pallor of the uterus and but little in the bladder. It has a strong action on all skin arteries and so far as I have seen on all medium sized arteries in the body. In the abdominal viscera its effect is great on the main branches of the coeliac and superior mesenteric arteries; the effect on the easily visible, though small, branches of these arteries in the stomach and intestines appears to me to be less than that on either the medium sized arteries or on the arterioles. The veins in these organs are little if at all affected.

On local application, similar but more marked effects are produced; thus distinct local pallor can be produced in the bladder; and in the stomach the pallor between the small strands of vessels may be so great as to suggest active contraction of the capillaries.

In the dog, pallor of the bucco-facial region is produced by supra-renal extract up to 10 c.c. (T. 1 in 6); this it will be remembered is the effect commonly produced by weak stimulation of the cervical sympathetic nerve, strong stimulation causing flushing.

<sup>1</sup> Spina, *Arch. f. d. ges. Physiol.* LXXVI. p. 204. 1899.

*Intestine.* It was noted by Boruttau<sup>1</sup> that supra-renal extract causes in the rabbit cessation, for some time, of the peristaltic movements of the intestine. This was confirmed by Pal<sup>2</sup>.

The effect in the rabbit is very striking in favourable cases, the peristaltic and the pendulum movements entirely cease. The inhibition is not necessarily synchronous with the pallor of the intestines, it may begin earlier or later, and so far as I have seen it always lasts longer. It must be noted however that when a particular loop of the intestine is much distended, as with bile, the strong contractions in it may be only partly inhibited by an amount of extract which completely inhibits the rest of the intestine.

After a single injection of 5 c.c. of extract (T. 1 in 6), the pendulum movements begin again in about five minutes, and the peristaltic movements somewhat later.

The supra-renal extract has a similar action in the cat, though the effect is generally less striking on account of the normally greater quiescence of the intestine.

Inhibition of large intestine is as marked as that of the small, and I have not observed any preliminary contraction.

*Œsophagus and stomach.* I have made some experiments on the rabbit by the method I have given earlier<sup>3</sup> for demonstrating the presence in the vagus of inhibitory fibres for the cardia. A tube containing salt solution is tied in the œsophagus, and connected with a vertical tube into which salt solution is driven when required. Contraction of the œsophagus is shown by a rise of fluid in the vertical or manometer tube, inhibition of the cardiac sphincter of the stomach by a fall of fluid.

The injection of supra-renal extract causes a rapid fall of the fluid in the manometer tube, *i.e.* the sphincter of the cardiac end of the stomach is inhibited. The time after the injection at which the fall begins is less the greater the amount of supra-renal extract and the more rapid the injection; thus if 1 c.c. of supra-renal extract (Tabloid 1 in 6) be injected in 10 seconds, the fall usually begins in 15 to 20 seconds; if 2 c.c. be injected in the same time the fall begins about the end of the period of injection. In these cases the fall takes the fluid within two or three centimetres of zero pressure, and is followed by a slight rise. When half a c.c. only of the supra-renal extract is

<sup>1</sup> *Arch. f. d. ges. Physiol.* LXXVIII. p. 113. 1899.

<sup>2</sup> Quoted from Lewandowsky.

<sup>3</sup> *This Journal*, XXIII. p. 407. 1898.

injected, there may be only one slight opening of the sphincter, causing a fall of a few centimetres only in the manometer. With large doses, the inhibition of the sphincter lasts for some minutes, and a large amount of fluid can be passed into the stomach at a low pressure. The effects of a given dose vary somewhat in different rabbits.

I have not observed any preliminary rise of fluid in the manometer on injecting supra-renal extract. Ordinarily the variations in the level of the fluid caused by the respiratory movements make a slight rise difficult to observe. If curari be given, these variations can be got rid of by suspending the respiration for 20 to 30 secs. There are still the spontaneous contractions of the œsophagus, but at times these are very slight; in such circumstances the primary effect of injecting supra-renal extract is a fall of pressure. And when the water-pressure in the œsophageal tube is reduced to a few centimetres there is no primary rise on injecting supra-renal extract. Stimulation of the peripheral end of the vagus after curari has been given causes (*op. cit.*) a marked rise of pressure with or without a secondary fall.

In one experiment when curari had been given there was a long period—two, three or more minutes—between the injection of 3 to 5 c.c. of the extract and the fall of pressure. This suggests some motor effect on the sphincter opposed to the inhibitory effect, but it may only have been due to an unusually strong normal tonic contraction. After injection of 20 mgrms. of atropin, the fall of pressure promptly followed the injection of extract. In all the experiments both the vagi were cut.

So far as I have seen, the effects of stimulating the peripheral end of the vagus are not modified in any essential point by injection of supra-renal extract, though a temporary diminution of the motor effect may apparently occur.

A dose of nicotine sufficient to abolish both the motor and inhibitory action of the vagus does not appreciably diminish the inhibitory action of supra-renal extract.

When the stomach is exposed and observed during injection of supra-renal extract, it is seen that such movements of the stomach as are occurring at the time are inhibited (rabbit and cat). The inhibition of the cardia in the rabbit is also obvious: the cardia bulges towards the end of the œsophagus, in the way characteristic of its inhibition; it stays in this state for a minute or two after injecting 5 c.c. of extract (T. I in 6), then some rhythmic contractions occur; in the cases I have noticed these contractions were much weaker than the after-contraction occurring after vagus-inhibition of the cardia.

The effect on the cardia and the rest of the stomach closely

resembles that produced by stimulating the splanchnic nerve, and not that produced by stimulating the vagus.

*Rectum and anus.* Supra-renal extract does not cause contraction of the recto-coccygeal muscle, nor the other effects on the rectum which are caused by stimulating the pelvic nerve. In the rabbit, the extract causes inhibition of the internal anal sphincter, and pallor of the mucous membrane; with 5 c.c. of extract (T. 1 in 6), the inhibition lasts one or two minutes, the pallor two or three minutes. There is no marked after-contraction. In the cat and dog the extract causes slight contraction of the sphincter with great pallor.

The effect in the several animals resembles in kind that produced by stimulation of sympathetic nerve-fibres<sup>1</sup>; but in the rabbit the inhibitory action is rather more marked, in the cat and dog considerably less.

*The bladder.* Lewandowsky<sup>2</sup> found that on passing a tube into the bladder the internal pressure was decreased by injecting supra-renal extract into a vein. The experiment I have tried in the cat. The result is striking. In 10 to 15 seconds from the beginning of the injection the pressure falls to about zero. Even a 0·5 c.c. of the extract (T. 1 in 6) will cause a quick fall of fluid in the tube connected with the bladder; during the fall the spontaneous contractions are diminished or stopped. On injection of 3 c.c. of extract the effect lasts for two or three minutes, then the pressure rises and the spontaneous contractions become large. Like other supra-renal effects the inhibition can be obtained an indefinite number of times. So far as I have seen there is no preliminary rise of pressure such as is produced by stimulating the hypogastric nerves.

Sympathetic inhibitory fibres for the bladder were described by myself in 1890. I found, by the manometer method<sup>3</sup>, that stimulation of the white rami to the inferior mesenteric ganglion or of the hypogastric nerves caused a fall of pressure after (usually) a primary rise. Griffiths<sup>4</sup> independently obtained similar results; and similar results were also obtained by Anderson and myself<sup>5</sup> and by Stewart<sup>6</sup>. Anderson and myself however, watching the bladder itself not under pressure from the manometer tube, were unable to observe any considerable degree of flaccidity following stimulation of the hypogastric nerves, so that we considered the inhibitory fibres, of the nature of other known inhibitory fibres, could only be few. The facts described by Anderson and myself

<sup>1</sup> Cp. Langley and Anderson. *This Journal*, xviii. p. 75. 1895.

<sup>2</sup> *Centralb. f. Physiol.* xiv. p. 433. 1890.

<sup>3</sup> Langley. *This Journal*, xii. 1890 (*Proc. Physiol. Soc.* xxiii.).

<sup>4</sup> Griffiths. *Journ. Anat. and Physiol.* xxix. p. 74. 1895.

<sup>5</sup> Langley and Anderson. *This Journal*, xix. p. 75. 1895.

<sup>6</sup> Stewart. *American Journ. Physiol.* ii. p. 182. 1899.

I have repeatedly observed, the contracted bladder does not become flaccid on stimulating the hypogastric nerves. The manometer methods, however, show that inhibitory fibres of a kind are always present. In recent experiments I find that if the stimulation of the hypogastric nerves is kept up for two or more minutes, the fall of pressure begins in about a minute, and for two or three minutes after the end of the stimulation the fluid passes readily into the bladder, and thus a very considerable distension can be produced.

On local application of supra-renal extract to a portion of the bladder, there is at first contraction of the part to which the extract is applied, and of more or less of the rest of the bladder; in a minute or so the local contraction gives way to local inhibition, and the part to which the extract has been applied bulges out.

*Internal generative organs.* In the rabbit, supra-renal extract causes strong contraction and pallor of the vagina and uterus (resp. uterus and its cornua) in the female, and of the vas deferens and seminal vesicles (resp. uterus masculinus) in the male. A small dose, about 1 c.c. of tabloid solution 1 in 6 is sufficient, and the result can be obtained repeatedly. In the cat there is great pallor and some contraction, the latter varying greatly in different individuals.

*External generative organs.* Supra-renal extract causes contraction and pallor of the external generative organs, both in the rabbit, the cat and dog; the effect may last five or more minutes. In the rabbit the skin over the penis and anus contracts in the manner described by Anderson and myself<sup>1</sup> as occurring on stimulation of the lumbar sympathetic. All the effects are less strong than those caused by sympathetic stimulation.

*Scrotum.* In the rabbit the extract causes pallor of the scrotum, but the main vessels do not completely contract. In the cat there is also pallor, and perhaps a trace of contraction of the tunica dartos. So far, however, as I have seen, there is never the marked contraction that can be caused by stimulating the lumbar sympathetic.

*Erector muscles of the hair.* According to Lewandowsky<sup>2</sup>, supra-renal extract causes in the cat contraction of the erector muscles of the hairs. He found that the effect lasted for hours after local subcutaneous injection.

I find that supra-renal extract when injected into the blood in small or moderate doses has no effect upon the hairs; when a large dose is given, a 5 c.c. of a 1 p.c. extract, there is often no effect, but there is sometimes on careful inspection a very slow and slight

<sup>1</sup> This *Journal*, xix. p. 91. 1895.

<sup>2</sup> *Centralb. f. Physiol.* xiv. p. 433. 1890.



movement. With larger doses a slow but distinct movement of hairs takes place, but on repetition of the dose the effect is either less or absent. Commonly the movement is so slow that it is not actually seen, but at the end of a minute or two some hairs are found to be above the level of the others. The effect is never comparable to that normally produced by stimulating the pilo-motor nerves, by injecting a few milligrams of nicotine, or to that occurring after death.

Nor do I find that sub-cutaneous injection has more than a slight effect on the hairs. Thus 2 c.c. of extract (T. 1 to 3) injected under the skin over the sacral vertebræ in the mid dorsal line, has either no effect or causes only a slight slow and partial erection of the hairs; when it occurs, however, the position of the hairs may be fairly persistent.

In the experiment already mentioned (p. 242) in which the post-ganglionic fibres of the superior cervical ganglion were allowed to degenerate, injection of supra-renal extract caused the usual slight erection of hairs in the face area. So far as is known, there are no pilo-motor nerves outside the sympathetic system; consequently the contraction of the arrectores pilorum must be due to a direct action on the unstriated muscle.

*Respiration.* As described by Oliver and Schäfer, and by subsequent observers, supra-renal extract causes temporary shallowing or cessation of the respiration. The effect is nearly always most marked with the first injection; with repeated injections the effect as a rule soon becomes trivial, and always becomes so if the injections are repeated a sufficient number of times.

*Injection of supra-renal extract after nicotine.* After injection of nicotine up to 100 mgrms., a small amount of supra-renal extract still causes all its customary peripheral effects, except that the irregularity in the heart-beat is less (cp. p. 247). The effect which the extract produces by way of the central nervous system on the respiration and on the heart-beat of course no longer occurs.

#### SUMMARY AND REMARKS.

Supra-renal extract causes a brief, but active secretion from the salivary and lachrymal glands, and this is unaffected by degeneration of the post-ganglionic fibres of the superior cervical ganglion. It will cause a secretion from the sub-maxillary gland after atropin has been given in sufficient quantity to paralyse the chorda tympani, and the

secretion occurring is increased by stimulating the chorda tympani. But after a large dose of atropin, injection of supra-renal extract into a vein does not cause a secretion. Apparently there is a mutual antagonism between the two substances.

It causes a primary moderate pallor of the gland, followed by a moderate flushing, and these effects are obtained after degeneration of the post-ganglionic fibres of the superior cervical ganglion. It causes also some secretion from the mucous membranes; an increase followed by a decrease in the flow of bile, possibly in consequence of variations in blood-pressure and blood-flow; it does not cause secretion from the pancreas if this gland is not secreting at the time, but it may increase a secretion already going on; it does not cause, so far as I have seen, secretion from the sweat glands of the foot of the cat.

The extract, as shown by Boruttau, causes inhibition of the intestine, and as shown by Lewandowsky, it causes inhibition of the urinary bladder. It causes also inhibition of the cardiac sphincter of the stomach, the stomach itself, and of the gall-bladder.

It causes in the cat, as shown by Lewandowsky, dilation of the pupil, protrusion of the eye, retraction of the nictitating membrane, and separation of the eyelids, and as also shown by Lewandowsky, these effects are produced after degeneration of the post-ganglionic fibres of the superior cervical ganglion. They are not prevented by ligature of the short ciliary nerves. In the dog, the extract however may cause slow contraction of the pupil with little or no other eye effects; the cause of the contraction has not been determined.

It causes contraction and pallor of the uterus, vas deferens, seminal vesicles, etc.; the contraction being especially marked in the rabbit.

As shown by Lewandowsky it causes contraction of the muscles of the hairs, but the effect is slight compared with the effects mentioned above, and with moderate doses is often absent.

It causes dilation with pallor of the end of the rectum and internal sphincter in the rabbit, and slight contraction with great pallor in the cat and dog.

Its action on the arteries is unequal, it acts relatively more on the medium sized arteries of the abdominal viscera than on the small but easily visible ones in the viscera (save the spleen), but it causes great constriction of very small vessels, either arterioles or capillaries. It has a comparatively slight action on the vessels of the bladder. It causes great contraction of both large and small sub-cutaneous arteries. That Oliver and Schäfer, Szymonowicz and Cybulski, and others have

observed general contraction of blood vessels and rise of blood-pressure hardly needs mention. The extract does not appear to cause any contraction in the general veins of the body.

It does not cause any marked contraction of the tunica dartos of the scrotum (cat), but it may perhaps have a trivial effect.

The effects produced by supra-renal extract in the cat and rabbit may be arranged roughly in the following order as regards the amount of extract required per body weight to produce an obvious effect.

Rise of blood-pressure.

---

Inhibition of the sphincter of the stomach and of the intestine (rabbit).

Inhibition of the bladder.

Dilation of the pupil (cat).

|  |                         |
|--|-------------------------|
| Withdrawal of nictitating membrane (cat) | } slightly less readily |
| Separation of the eyelids (cat)          |                         |

---

Contraction of uterus, vas deferens, seminal vesicles, etc. (rabbit).

Salivary and lachrymal secretion.

Inhibition of the stomach.

Inhibition of the gall-bladder and increased bile secretion.

Dilation of pupil (rabbit).

Inhibition of internal anal sphincter (rabbit).

|   |                      |
|---|----------------------|
| Contraction of internal anal sphincter (cat)    | } effects relatively |
| Contraction of internal generative organs (cat) |                      |

---

Contraction of the muscles of the hairs.

---

|   |                      |
|---|----------------------|
| Contraction of tunica dartos of scrotum | } no certain effect. |
| Secretion of sweat                      |                      |

The foregoing account accentuates the fact already known, that supra-renal extract varies in its action on unstriated muscle, some it causes to contract, some it inhibits, and on some it has little or no effect.

I have formerly divided the autonomic nervous system into sympathetic, cranial, sacral, and enteric. It is a noteworthy fact that the effect of supra-renal extract in no case corresponds to that which is produced by stimulation in normal conditions of a cranial autonomic or of a sacral autonomic nerve. It does not produce the effect of stimulating the 3rd nerve on the eye, nor of the vagus on the stomach

or the heart, nor the effect of stimulating the pelvic nerve on the bladder, the rectum, the anus, or the generative organs. It is true that it causes a free secretion of saliva, but the secretion is not accompanied in its first stages by increased vascularity such as is caused by stimulation of the chorda tympani or of Jacobson's nerve.

It is equally noteworthy that the effects produced by supra-renal extract are almost all such as are produced by stimulation of some one or other sympathetic nerve. In many cases the effects produced by the extract and by electrical stimulation of the sympathetic nerve correspond exactly.

The view which obviously presents itself to account for these facts is that the supra-renal extract has a specific stimulating action on sympathetic nerve-endings, having little or none on cranial and sacral autonomic nerve-endings, and that the degree of stimulation varies with the nerve-endings in different tissues. But some results mentioned above run counter to this view; they are, the continued activity of the extract upon the eye and upon the blood vessels of the submaxillary gland, and on the erector muscles of the hair after degeneration of the post-ganglionic sympathetic nerves. It is hardly possible to avoid the conclusion that in these cases the extract acts directly on the unstriated muscle, and if this is so, it is probable that in all cases the action is direct. And it will be remembered that it has been shown by Oliver and Schäfer and by Boruttau, that the action is direct on somatic striated muscle.

In such case the difference in action on different autonomic tissues must depend upon their intrinsic differences; and this takes out of our reach any immediate hope of explanation why the action in the several cases should correspond so closely with that caused by stimulation of the sympathetic nerves. The theory of direct action cannot, however, be regarded as more than provisional until it is shown experimentally that the inhibitory action of supra-renal extract on certain unstriated muscle, and its stimulating action on salivary gland cells take place in the absence of nerve-endings. These points I propose to consider in a later paper.