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8

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By H. H. DALE.

(*From the Wellcome Physiological Research Laboratories, Herne Hill.*)

A PRELIMINARY note on the phenomena dealt with more completely in this paper was entitled, "The Physiological Action of Chrysotoxin[1]." Since the date of that publication further experiment has shown that the action is due to a principle, or combination of principles, which, by the aid of the physiological test, can be recognised in the various substances for which the title of "active principle" has been claimed, and indeed in all preparations of ergot possessing therapeutic activity. The active resin extracted from chrysotoxin, and called by Jacobj[2] "sphacelotoxin," gives the effect in doses of a few milligrammes. So also do preparations corresponding in mode of extraction and solubility to the "cornutine" of Kobert, and differing from that substance only in their failure to elicit the spasms in frogs, described by Kobert[3] as characteristic—a failure by no means unique in the experience of those who have worked with "cornutine" since Kobert. A resinous substance separated from commercial ergotinine also gives the reaction very typically and in small dosages; while, in larger quantities, many specimens of the ordinary pharmacopœial extracts produce the same effects, complicated only by the presence of depressant impurities.

These facts make it impossible to speak of the action any longer as that of chrysotoxin. On the other hand, the wide acceptance of Kobert's[4] view as to the difference between sphacelotoxin (in sphacelinic acid) and cornutine would render the attribution of the effects to either of those substances misleading. The introduction of new names on the strength of physiological results, and in default of chemical isolation of principles, would inevitably add to the existing confusion,

[1] *Proc. Phys. Soc.* p. lviii. 1905. (This *Journal*, xxxii.)
[2] *Arch. f. exp. Path. u. Pharm.* xxix. p. 85. 1897.
[3] *Arch. f. exp. Path. u. Pharm.* xviii. p. 316. 1884.
[4] *loc. cit.*

and I have thought it better to speak of the action as that of "ergot," and to mention in the body of the paper the particular preparations used. This seemed the more desirable in view of the possibility that the effects are due, not to one but to two closely associated principles. Dr G. Barger is investigating the matter from the chemical side, and in a later joint paper we hope to deal with the nature of the active substance or substances, their distribution in ergot preparations, and the therapeutic application of our results. This paper is concerned with the action only in so far as it appears to be of general physiological interest.

Since the various preparations used in the experiments here described, while free from ergotinic acid, choline and the other depressant impurities of galenical preparations, contain varying proportions of inert matter, it will be understood that indications as to dosage can be no more than rough approximations. Chrysotoxin, which generally contains about 99% of inactive but harmless material, was the form of administration in all the earlier experiments. In many cases the chrysotoxin was dissolved in the smallest possible volume of ethyl alcohol, just enough sodium hydrate added to prevent precipitation on the addition of water, and the solution then diluted with water to a strength of 1% chrysotoxin. In other cases the preformed water-soluble sodium salt was used, prepared by precipitation from a solution in dry ether by means of sodium ethylate. This preparation possesses a good deal of the activity of the original chrysotoxin, but not all, nor even a constant proportion of it. Preparations corresponding to Jacobj's sphacelotoxin and to Kobert's cornutine were used in many of the later experiments, and were similarly dissolved in dilute sodium hydrate. Their activity varied from 20 up to 100 times that of the average specimen of chrysotoxin.

The experiments here discussed are concerned only with such prompt effects of intravenous injection as can be observed directly, or with the aid of mechanical methods of recording, in the anæsthetised or pithed animal. No new observations have been made on the slowly developed effects of administration by the mouth or hypodermically to the intact animal, and these will be dealt with only incidentally. Most of the experiments were made on cats: a few also on rabbits, dogs, monkeys, ferrets, and fowls, the purpose for which each species was used being indicated in dealing with the results of particular experiments. The animals were always anæsthetised with chloroform, ether, or A.C.E. mixture, unless or until the cerebrum was pithed.

The effects of intravenous injection, the mode of administration used throughout these experiments, are divisible into two classes, corresponding to a primary or stimulant, and a secondary or paralytic stage of the drug's action. It will be convenient, however, as giving a more connected picture of the sequence of events, to deal, in the first place, separately with each organ or system on which observations have been made.

1. The Circulatory System.

Primary or stimulant action. The first definite laboratory demonstration of the stimulant effect of ergot on the peripheral arteries was given by Kobert[1]. The gangrenous phenomena which he observed in the comb and other peripheral structures of the fowl and the pig, as the result of administering sphacelinic acid, were attributed by v. Recklinghausen, who investigated the phenomena histologically, to "powerful and persistent constriction of the arterioles." In contrast to this repeatedly confirmed and now familiar action on the cock's comb, the results of observing the effect on blood-pressure have been very variable and unsatisfactory. Setting aside, as merely misleading, the numerous observations on the depressant effect of crude extracts given intravenously[2], the recorded results with such comparatively pure preparations as sphacelotoxin and cornutine are surprisingly inconclusive. Kobert gave an intravenous injection of the sodium salt of sphacelinic acid to a rabbit and observed a rise of blood-pressure, beginning 8—10 minutes after the injection, followed by strychnine-like spasms of the whole animal and cessation of respiration, with which the blood-pressure fell rapidly. In a rabbit deeply chloralised, or with the cord cut in the neck, he observed no trace of these phenomena. This description may well raise a doubt as to whether the whole phenomenon be not asphyxial in origin: but that supposition seems to be excluded by the fact that Kobert observed a larger rise of pressure in a curarised rabbit with artificial respiration. Under the same conditions he observed a rise of pressure with cornutine.

Jacobj[3], who obtained with his preparations similar effects on the cock's comb to those observed by Kobert, found but slight effects on

[1] *loc. cit.*

[2] Cf. a recent paper by Sollmann and Brown (*Journal American Med. Assoc.* July 22, 1905), who give references to most of the papers dealing with similar experiments.

[3] *loc. cit.*

the blood-pressure of rabbits and cats as the result of intravenous injection. It is noteworthy that, in contrast to Kobert, Jacobj only obtained a rise of blood-pressure of any significant magnitude in a cat with the spinal cord cut in the neck.

Santesson[1], experimenting with a preparation called "cornutine" by Keller, and with pharmaceutical extracts, obtained a significant rise of pressure only in the fowl. In rabbits the first dose caused a slight rise, subsequent doses a fall of pressure.

In experiments in which I have used a cat breathing naturally, under ether, the effects of intravenous injection have been similarly irregular and unsatisfactory, the usual result of an intravenous injection of chrysotoxin, sphacelotoxin, or cornutine being a small preliminary rise of blood-pressure, giving way, as respiration fails, to a prolonged fall. The respiration becomes hurried and very shallow, and may finally cease altogether; the central origin of the paralysis being proved by the unimpaired response of the diaphragm to stimulation of the phrenic nerves. A phenomenon may be mentioned here which is described by Jacobj as characteristic of his "secalintoxin[2]," and which I have seen several times with chrysotoxin and other preparations. If, when the blood-pressure has fallen to a low level as a result of the respiratory paralysis, artificial respiration be applied, the pressure rises rapidly to a level considerably above the original. Any intermission of artificial respiration now causes an immediate and steep fall of pressure, giving way again to a rapid rise when the respiration is resumed. The significance of this effect will become obvious at a later stage: its immediate importance is to indicate the necessity of using an animal already under artificial respiration if the effects of these substances from ergot on the circulatory system are to be studied in an uncomplicated form by recording the blood-pressure. Suitable conditions are afforded either by the use of curare, combined with a volatile anæsthetic, or by pithing the brain and medulla oblongata. The latter was effected either directly, through the occipito-atlantal membrane, or by performing tracheotomy and exposing the cord at the second cervical vertebra under chloroform and ether, cutting across the cord at this level and completely destroying the brain with the cord above the section. In a cat, prepared by any of these methods, under artificial respiration, and with cut vagi, unless the medulla oblongata was destroyed

[1] *Skandinav. Arch. f. Physiol.* XIII. p. 107. 1902.

[2] Stated by Jacobj to be a compound of "sphacelotoxin" with the inactive alkaloid "secalin."

the effect of sphacelotoxin and similar preparations is very striking. Fig. 1 shows the effect of injecting 20 mgms. of the sodium salt of chrysotoxin, dissolved in 2 c.c. of water, into the jugular vein. It will be seen that the rise of pressure begins a few seconds after the injection and develops rapidly, so that the maximum is reached in 1—2 minutes. The actual rapidity of the rise and its persistence vary very greatly in different individuals. I have seen an effect of 10 mgms. of chrysotoxin lasting more than 30 minutes. Larger doses produce, on the whole, a higher and more rapid but less persistent rise of pressure than smaller ones. A point of some little interest is illustrated by Fig. 2; viz. that when a large dose of the drug is given the respiratory ventilation must be unusually vigorous for the pressure to show the normal sustained rise.

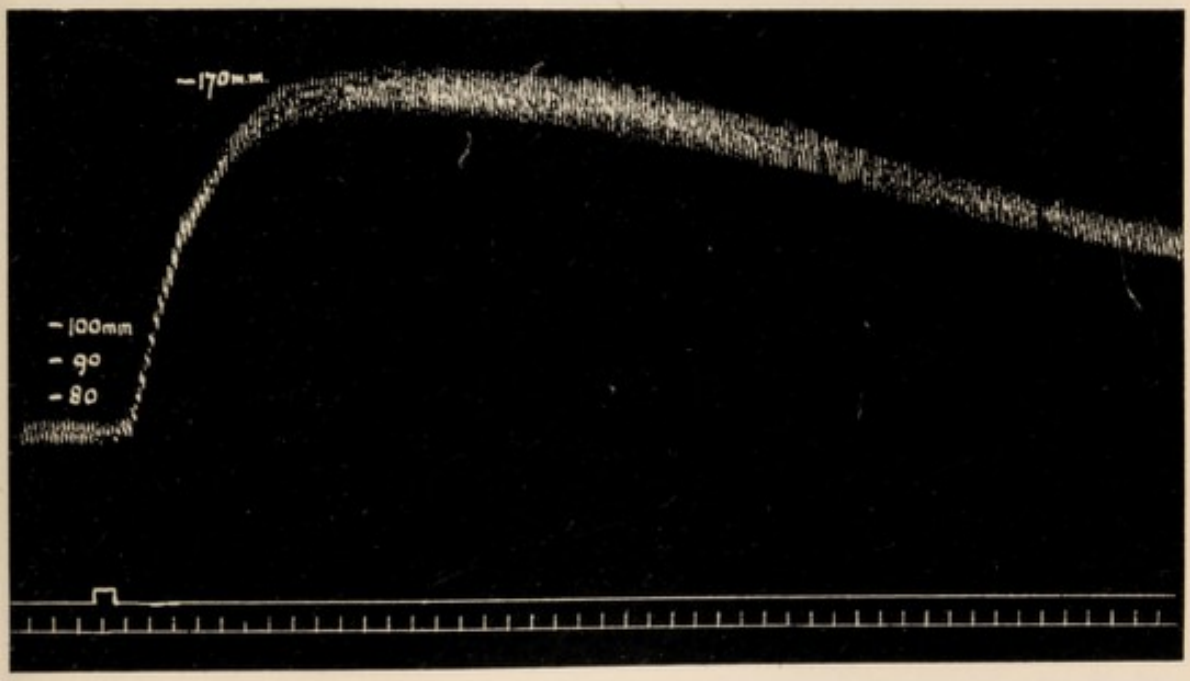

Fig. 1. $\times \frac{1}{3}$ linear. Effect, on blood-pressure of a pithed cat, of injecting 20 mgms. of the sodium salt of chrysotoxin intravenously.

In the case illustrated in Fig. 2 the first rapid rise, caused by injection of 50 mgms. of sodium chrysotoxin, soon gave way to a fall, which was increasing in rapidity when it was arrested by narrowing the side-valve of the tracheal cannula and increasing the volume of the respiratory inflation. The effect is evidently of the same nature as the fall of blood-pressure with stoppage of respiration, and its rapid recovery on resumption, described by Jacobj and already mentioned. The constricting effect of ergot on the pulmonary vessels, described by several observers[1], suggests itself as possibly concerned in the matter.

[1] Cf. Plumier, *Journ. de Phys. et Path. générale*, VII. p. 13. 1905.

As to the cause of the rise of systemic pressure, the plethysmographic tracing from a cat's leg, shown in Fig. 3, indicates peripheral vaso-constriction as at least a principal factor. A similar tracing is given by a plethysmograph containing a loop of small intestine: so that the arterial constriction is widely spread through the system.

The effect on the heart is variable. An initially slow beat is at first quickened, and the rise produced may, as in Fig. 2, be practically as

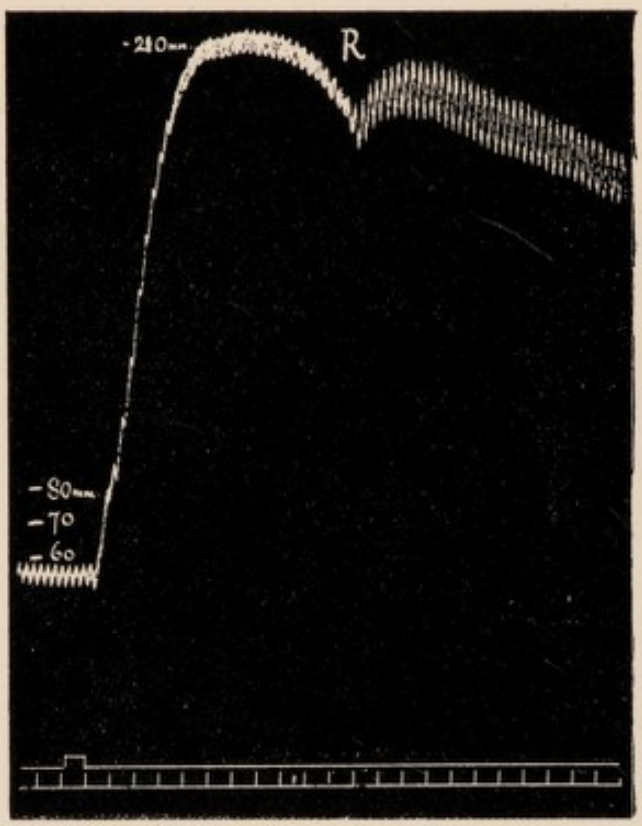

Fig. 2.

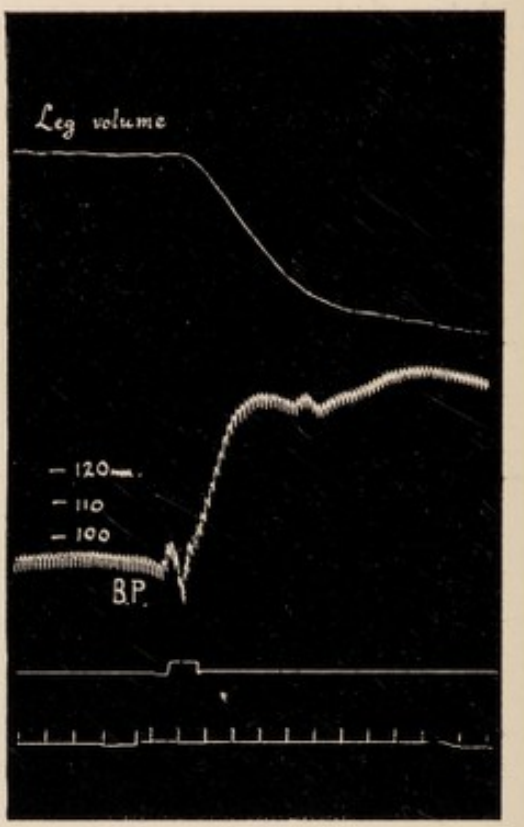

Fig. 3.

Fig. 2. $\times \frac{1}{3}$. Effect of 50 mgms. of chrysotoxin on blood-pressure of a pithed cat. At *R* the side valve of the tracheal cannula was narrowed so as to increase the volume of the artificial respiration.

Fig. 3. $\times \frac{1}{3}$. Effect of 20 mgms. of chrysotoxin on blood-pressure and leg volume of cat under ether and curare, with artificial respiration.

abrupt as that produced by adrenaline. A secondary slowing often occurs, and is not abolished even by large doses of atropine. When, in an animal with intact medulla, the vagi are uncut, the reflex cardiac slowly prevents any marked rise of blood-pressure. Even with cut vagi, or with the medulla destroyed, a frequent effect of the drug, when the heart-beat is rapid and feeble, is to cause slowing and augmentation. Changes in the heart-beat are, therefore, an inconstant factor in the

rise of systemic pressure. In a dog similarly prepared the effect is very similar—a large and lasting rise of systemic pressure, mainly due to peripheral vaso-constriction. In the rabbit and the monkey, on the other hand, I have been unable to detect more than a trace of pressor effect. In the rabbit, indeed, the primary stimulant effects of the drug on any organ appear very slight by comparison. The pressor effect is well marked in the fowl.

It is quite evident that this rise of blood-pressure is a different phenomenon from that described by Kobert. We have here a rise of pressure seen well in the cat and dog, scarcely present at all in the rabbit, immediate in onset, prolonged in duration, and quite independent of the vaso-motor centre: that described by Kobert was marked in the rabbit, slight in the dog, began 8—10 minutes after injection, and was abolished by section of the cord and by chloral. Whatever be the explanation of Kobert's observations, there can be no doubt that we are here dealing with a true expression of the primary vaso-constrictor action of the drug. Discussion of the mode of its action may be postponed for the present.

Secondary or paralytic stage. Since my preliminary note was published Sollmann and Brown[1] have independently observed, in the dog, an obliteration of the pressor effect of adrenaline by intravenous injection of large doses of liquid extract of ergot. The phenomenon, as they describe it, is merely a diminution of the adrenaline rise of pressure, amounting, in some cases, almost to extinction. Their observation on the spleen, referred to in the next section, leaves, however, no room for doubt that they had produced, in an imperfect form, the effect now to be described.

To exhibit this paralytic effect on the vascular system in its most striking form a large dose of an active preparation of ergot is given intravenously to a pithed cat. If, before the resulting rise of pressure has subsided, adrenaline[2], nicotine, or a further dose of chrysotoxin, etc., be injected, the effect is in each case a fall of blood-pressure in place of the customary rise (Fig. 4), lasting like the latter for a time proportional to the dose given. With most specimens of chrysotoxin 50—100 mgms.

[1] *Journal of the American Medical Association*, July 22, 1905.

[2] In accordance with physiological custom the name "adrenaline" is used throughout this paper to denote the active principle of the supra-renal gland, in whatever form administered. Simple extracts of the gland, commercial preparations issued under various "brand" names, and solutions of the pure base, without preservative, were all used, and all give the effects described.

is sufficient to produce this reversal of the effect of adrenaline: of Jacobj's sphacelotoxin I have had specimens which would produce it in a dose of 2 mgms.; and 1 mgm. of a preparation corresponding to Kobert's cornutine was similarly effective. A repetition of a small dose

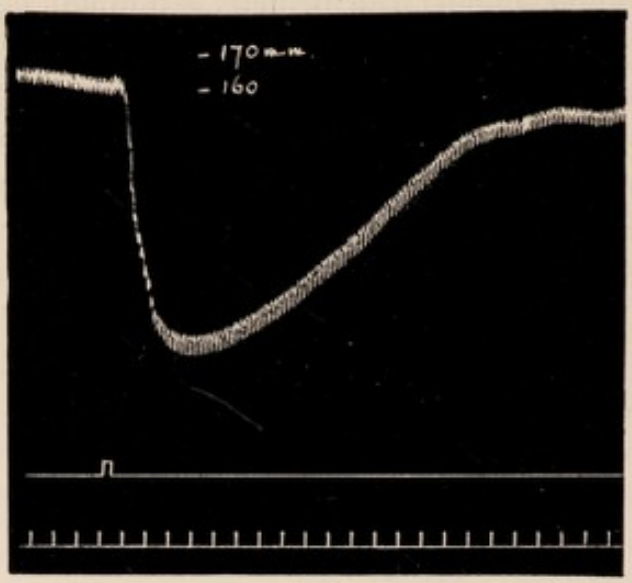

Fig. 4. × ½. Effect on blood-pressure of 0·1 mgm. adrenaline intravenously, after 5 mgms. of cornutine.

of adrenaline or nicotine causes a repetition of the depressor effect. With large doses—*e.g.* 1 mgm. of adrenaline—the fall is proportionately longer, and a fresh injection, while the effect of the first persists, causes

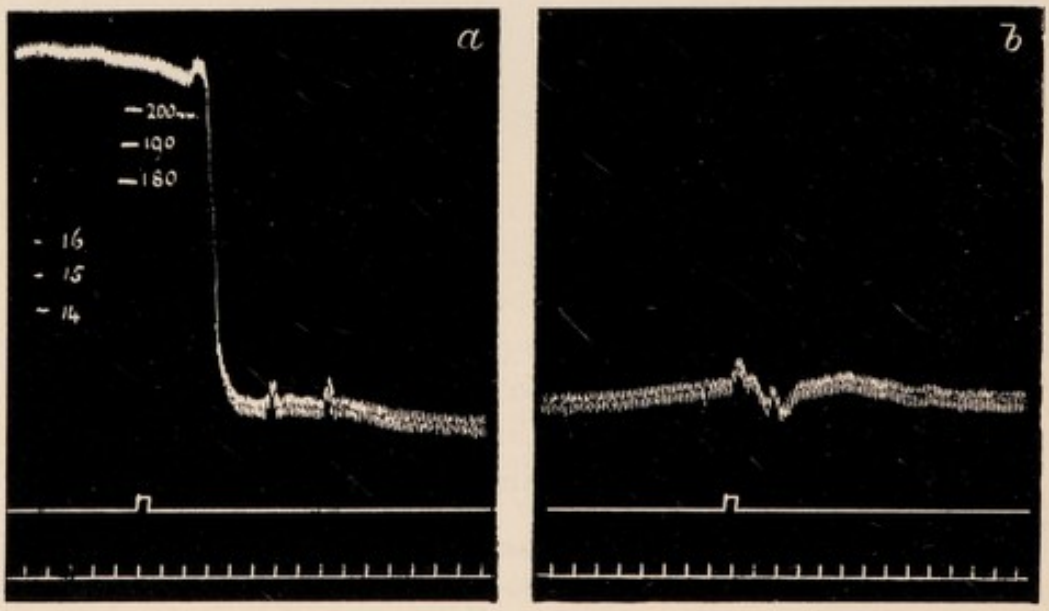

Fig. 5. × ½. Effect of 2 successive injections each of 1 mgm. of adrenaline, after 10 mgms. of active resin extracted from commercial ergotinine. Between (*a*) and (*b*) tracing corresponding to 2 minutes has been cut out.

either no effect or a slight further fall (Fig. 5). Stimulation of the splanchnic nerves (Fig. 6) or of the spinal cord causes a quite similar fall of pressure. On the other hand, barium chloride (Fig. 7) and pituitary extract (see Fig. 26) produce the usual rise.

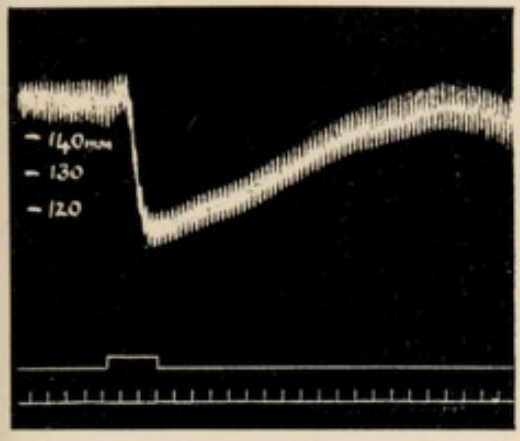

Fig. 6.

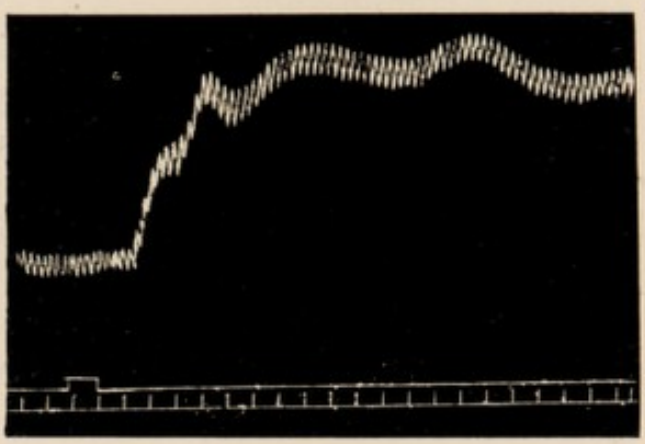

Fig. 7.

Fig. 6. $\times \frac{1}{3}$. Effect on blood-pressure of stimulating the left splanchnic nerve (coil at 10 cm.) after 100 mgms. of chrysotoxin.

Fig. 7. $\times \frac{1}{3}$. Effect on blood-pressure of 5 mgms. of $BaCl_2$, after 150 mgms. of chrysotoxin.

If small successive injections of the drug be given—*e.g.* 10 mgm. doses of chrysotoxin—and the effect of adrenaline tested after each, the progress of the change can be followed. The adrenaline rise first becomes reduced in height and prolonged in duration. Usually at this stage there is an initial rapid rise of about 20 mm., after which the ascent becomes abruptly slower, so that the curve has the form of a long, ascending plateau, to which succeeds a gradual decline. At a later stage of the paralysis adrenaline causes a brief initial rise, succeeded by a fall, which may be merely relative to the rise, or may carry the pressure actually below the level at the time of injection: this fall again gives way to a long, slow, secondary rise and decline. The further progress of the paralysis is marked by increasing prominence of this depressor phase of the adrenaline effect, with progressive extinction of the initial and secondary rises, until, finally, a purely depressor reaction is left.

The complete reversal is attained earlier for small quantities of adrenaline, such as 0·05—0·1 mgm., than for larger doses, such as 1 mgm. or more. There is a stage at which 0·1 mgm. of adrenaline causes a pure depression, when 1 mgm. still causes a low, prolonged rise. A similar rise of pressure is produced at this stage by electrical

excitation of the splanchnics with any strength of current which is effective at all. Further injections of chrysotoxin then complete the paralysis, so that any amount of adrenaline—I have used up to 20 mgms. as a dose—and the strongest stimulation of the splanchnic nerves cause a simple fall of pressure.

A similar reversal of the sympathetic pressor effect was produced in the dog and the ferret[1], but the fall of pressure observed was in neither case so striking as in the cat. The necessary quantity of the ergot preparation was also relatively larger; a dog of about 15 kilograms requiring 10—20 times the amount which would complete the reversal in a cat of 2—3 kilograms.

It is of incidental interest to note that, when once the paralytic effect has been produced in the dog, any quantity of adrenaline may be injected without the ordinary danger of heart-failure, attributed by Elliott to intravascular clotting. If Elliott's conclusion is correct the clotting must be dependent on some action of adrenaline which ergot annuls: for, as we shall see, many of the effects of adrenaline are retained unaltered, so that the substance is not itself destroyed.

In the rabbit the fall of pressure with adrenaline was never obtained, the effect of ergot being, in this animal, a gradual weakening and ultimately an approximate abolition of the pressor effect of small doses of adrenaline. Even this required large doses of the drug—about 200—300 mgms. of active chrysotoxin.

The fowl is still more resistant to the paralytic action, and with chrysotoxin I never succeeded in producing more than a slight diminution of the sympathetic pressor effect. Recently, with a powerful specimen of cornutine giving vaso-motor reversal in the cat in a dose of 1 mgm., I succeeded, by giving 20 mgms. to a cock, in reducing the effect of 0·1 mgm. of adrenaline practically to *nil*, though 1 mgm. still gave a fair rise of blood-pressure. Adrenaline, directly applied in 1 in 1,000 solution, then failed to cause contraction of the jejunum. This resistance of the fowl is strongly suggestive in connexion with its special liability to the gangrene associated with ergot poisoning.

Some conclusions may be drawn at this stage as to the nature of the paralytic effect on the vascular system. The unaltered efficacy of barium chloride and pituitary extract must first be considered. The importance of the barium effect may be discounted by regarding it as due to a toxic rigor of the muscle fibres. This can hardly be urged in the case of pituitary extract. The effect of this can be repeated a number of times if sufficient

[1] Cf. Elliott. This *Journal*, xxxii. p. 412. 1905.

interval be allowed to elapse between the injections[1]. The fact that the action is retained unaltered, after doses of ergot preparations which entirely remove the normal pressor effect of adrenaline and sympathetic stimulation, establishes two important points. Firstly, it shows that the contractile elements in the muscle fibres of the arteries are still capable of responding by a normal contraction to an appropriate stimulus: so that it is not to any functional change in these elements that we must attribute the altered effect of adrenaline, etc. Secondly, and incidentally the conclusion may be drawn that the pressor principle contained in pituitary (infundibular) extracts produces its stimulant effect on the arterial muscle not through any part of the sympathetic nervous apparatus, not through the related structures on which adrenaline acts, but through some other structure or substance of the muscle fibres themselves.

The disappearance of the normal effect of adrenaline can, therefore, only be attributed either to destruction of that substance, or to paralysis of the structures normally affected by it. We have already mentioned, and shall shortly proceed to the evidence of the fact, that many of the effects of adrenaline are retained: therefore the motor structures through which it affects the arterial muscle fibres must be paralysed. This supposition, too, is the only satisfactory explanation of the parallel destruction of the pressor effects of nicotine and of exciting sympathetic nerve fibres. For a simple, progressive obliteration of the pressor effect, as seen in the rabbit, no further explanation is required. The case is different where, as in the cat and other carnivora, the ordinary rise of pressure is replaced by a fall almost as marked. That, in this case also, the sympathetic motor myoneural junctions[2] in the arterial walls are paralysed is obvious: but the actual depression remains to be accounted for. As a step towards this it is necessary, in the first place, to decide whether the fall of pressure is due to cardiac depression or to vaso-dilation. Unless very large doses of ergot preparations have been given the heart is still obviously accelerated and the beat certainly not weakened during the fall of pressure caused by adrenaline: moreover, stimulation of the peripheral ends of the splanchnic nerves, which causes a similar depression, cannot

[1] Cf. Schäfer and Vincent. This *Journal*, xxiv. p. xix. (*Proc. Phys. Soc.*). 1899.

[2] This term is used here in the sense in which it is employed by Elliott (this *Journal*, xxxii. pp. 434—436. 1905), to denote the structure which can be excited either by adrenaline or by impulses in sympathetic axons. If Langley's recent terminology be accepted (this *Journal*, xxxiii. p. 374. 1905), "receptive substance for adrenaline" must be substituted throughout for "sympathetic myoneural junction."

affect the heart. If any doubt remained it could be at once removed by a plethysmographic experiment, which shows that with the fall of pressure produced by adrenaline or splanchnic stimulation there is a concomitant increase in intestinal volume (Fig. 8). Direct inspection during the fall of pressure detects a slight flushing of the bowel: and the same is seen better by local application of adrenaline, which produces a slight local hyperæmia in place of the usual pallor. Vaso-dilation is thus directly proved to be the cause of the depressor effect,

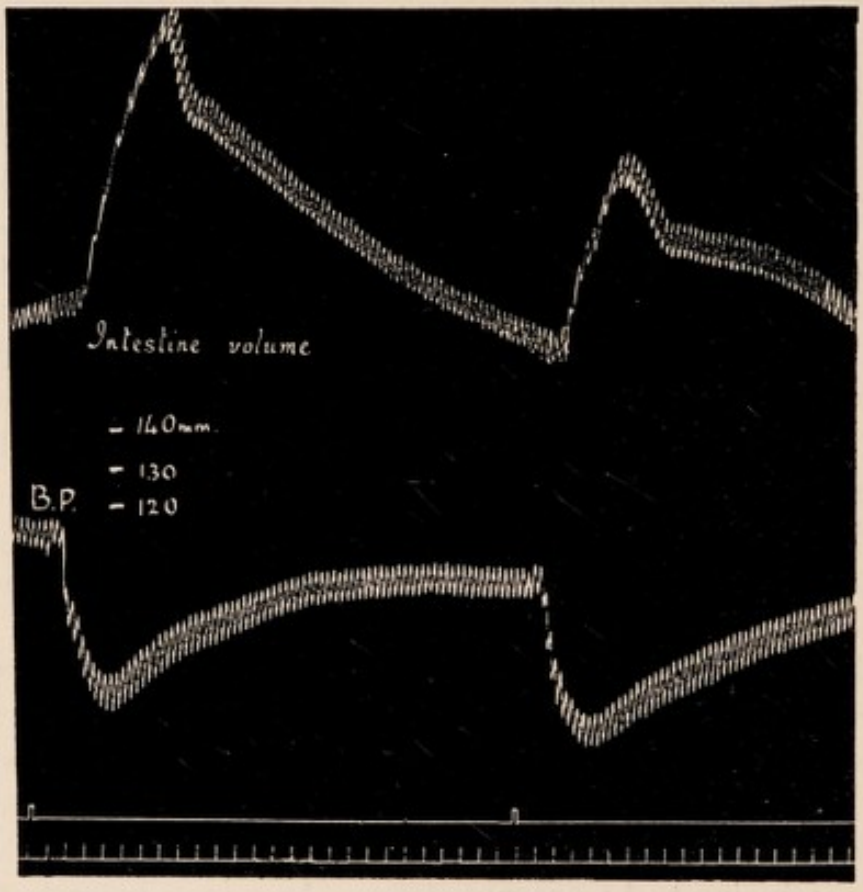

Fig. 8. ×¾. Fall of blood-pressure and concomitant increase of intestinal volume produced by 2 successive doses, each of 0·1 mgm. adrenaline, after 100 mgms. chrysotoxin.

and a cardiac origin of the phenomena excluded. This vaso-dilation, however, may be passively produced by relaxation of the intrinsic musculature of the intestinal wall. This, in the absence of vaso-constriction, would allow the intestine to become hyperæmic, diminish the peripheral vascular resistance, increase the total volume of the system, and might thus be responsible for the fall of blood-pressure. That the contractile abdominal viscera do still relax with adrenaline or stimulation of the splanchnics, after the ergot paralysis is complete,

will be shown later. But though this relaxation may, and probably does play some small part in the production of the phenomenon, it is certainly not the sole or the principal cause: for adrenaline still causes a marked fall of pressure when the whole of the contractile viscera have been removed from the abdomen, the liver being by this procedure necessarily excluded also from the circulation (Fig. 9).

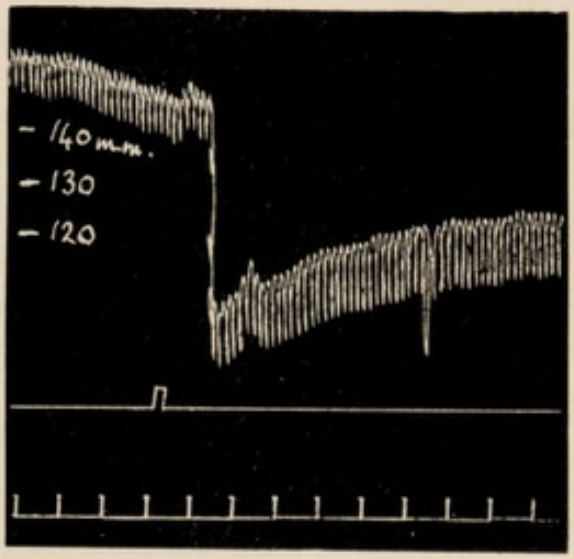

Fig. 9. Fall of blood-pressure produced by 0·1 mgm. adrenaline in a pithed cat in which the abdominal portion of the alimentary canal had been completely removed, after injection of 100 mgms. chrysotoxin.

The vaso-dilation can, further, be watched directly in the non-pigmented pads of the cat's foot. Stimulation of the abdominal sympathetic between the 4th and 5th lumbar ganglia caused marked pallor of the pads of the hind-foot of the same side. 5 mgms. of cornutine were then given intravenously and the stimulation repeated. The pads now became slightly, but distinctly pinker. A similar flushing was caused by injecting a few minims of 1 in 1000 adrenaline directly into the femoral artery.

We are thus left with one possibility only: the effect, which, as we have seen, is on the sympathetic myoneural junctions, must be of such a nature that the stimulus of adrenaline, or of impulses in sympathetic axons, causes relaxation of the muscular wall of the arteries in place of the normal constriction. A complete analysis of the effect can be made only by parallel considerations of the effects on other plain muscular structures: but a few other experiments illustrating the effect on the vascular system must first be mentioned.

After doses of ergot preparations, far in excess of those necessary to

convert the effect of any dose of adrenaline or of the strongest stimulation of the splanchnics into pure depression, stimulation of the chorda tympani causes the usual acceleration of blood-flow through the cat's submaxillary gland, as seen by the rate of hæmorrhage from a small cut vein draining the gland. Under the same conditions stimulation of the 2nd and 3rd sacral roots in the spinal canal caused a marked erection of the penis, not perceptibly different from that obtained before the ergot was given. The inhibitory effect of the vagus on the heart likewise suffered no trace of diminution: indeed, after large doses of ergot the inhibition seemed to be more complete with the weaker stimuli than before. With the secondary coil at 10 cm., for example, I obtained a very partial inhibitory effect from either vagus at the beginning of one experiment. After giving 150 mgms. of chrysotoxin a much more complete effect was obtained with the same strength of stimulus. This difference can probably be explained by removal of tonic accelerator impulses in the true sympathetic. However that may be, the fact of importance is that the cranial and sacral autonomic inhibitory nerves to the heart and arteries suffer no paralysis at any level.

The cardio-accelerator effect of adrenaline, as stated above, is not abolished by such doses of ergot as suffice to reverse the effect on the blood-pressure. With larger doses, however, the accelerator myoneural junctions also suffer paralysis, about 200—300 mgms. of active chrysotoxin being normally sufficient to complete the effect. There is here no question of reversal: neither by adrenaline nor by electrical excitation of the cardiac branches from the stellate ganglion have I succeeded in producing a slowing of the heart. The effect was, like that on the arteries of the rabbit, a simple progressive abolition of the action of the sympathetic fibres and of adrenaline.

2. The Spleen.

The observations were made on cats with the brain pithed. The spleen was enclosed in an air plethysmograph, registration being made by a large Hürthle piston-recorder. A preliminary dose of ·1 mgm. of adrenaline caused the usual rise of blood-pressure and contraction of the spleen. Two successive doses of chrysotoxin, of 50 mgms. each, were then given. Each injection caused a brief contraction succeeded by steady dilation of the spleen: and since the second injection caused no rise of blood-pressure above the level maintained after the first injection, the effects must be attributed to the chrysotoxin itself. The course of

events suggests a temporary excitation of the motor sympathetic supply to the spleen, followed by a blocking of the tonic motor impulses. After 100 mgms. or more of chrysotoxin, the fall of blood-pressure caused by an injection of adrenaline is accompanied by a small dilation of the spleen (Fig. 10). The same effect was observed by Sollmann

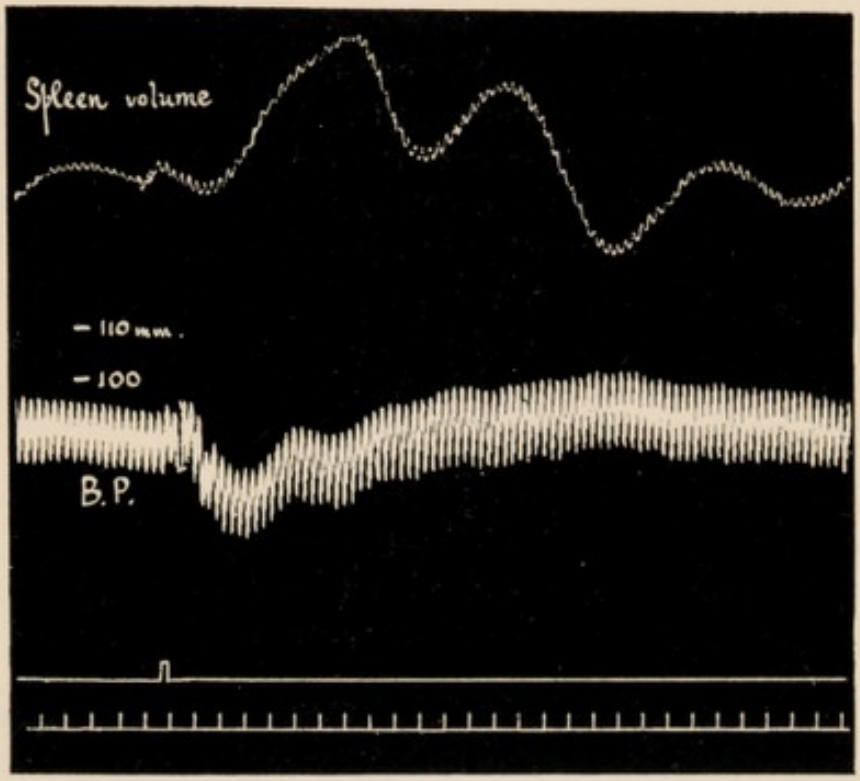

Fig. 10. Pithed cat. Blood-pressure and spleen-volume. Effect of 0·1 mgm. adrenaline after 100 mgms. chrysotoxin.

and Brown when they injected adrenaline directly into the spleen after very large doses of the liquid extract of ergot. Here, again, the motor effect of direct stimulation of the splenic nerve is far more resistant to the paralytic action than is that of adrenaline. Two or three times the dose of the ergot preparation must be given for reversal of this effect of direct stimulation of the nerve.

3. The Muscular Coats of the Intestines.

The action was observed in the cat, the dog, and the monkey, pithed or anæsthetised with A.C.E. or ether. The movements of the small intestine were observed by the balloon method, with a Hürthle piston-recorder or Brodie's bellows. Those of the large intestine were observed directly.

Stimulant stage. The effects were neither striking nor constant, and in any case difficult to interpret. In the dog, with both vagi and splanchnics cut, the pendulum movements of the small intestine showed, when 50 mgms. of chrysotoxin were given intravenously, a brief inhibition, followed by a permanent increase both of the tone of the muscle and the amplitude of the pendulum movements. In the cat a temporary increase of tone and a few powerful waves of peristalsis were sometimes produced: in other cases the effect was merely a slight increase of the amplitude of the pendulum movements. In the monkey (one experiment) a slight increase of tone was the only result. It is difficult to determine to what extent these effects are due to changes of blood-pressure in the pithed animal, or to the progressive asphyxia in the animal without artificial respiration. In any case they are comparatively slight. The same may be said of the movements of the large intestine, where some increase of peristaltic activity was all that could be observed.

Paralytic stage. After the largest doses of ergot administered—up to 500 mgms. of active chrysotoxin—the muscle of the intestinal walls responded by a quite normal inhibition to adrenaline or stimulation of the sympathetic nerves. Fig. 11 shows a record of the inhibitory

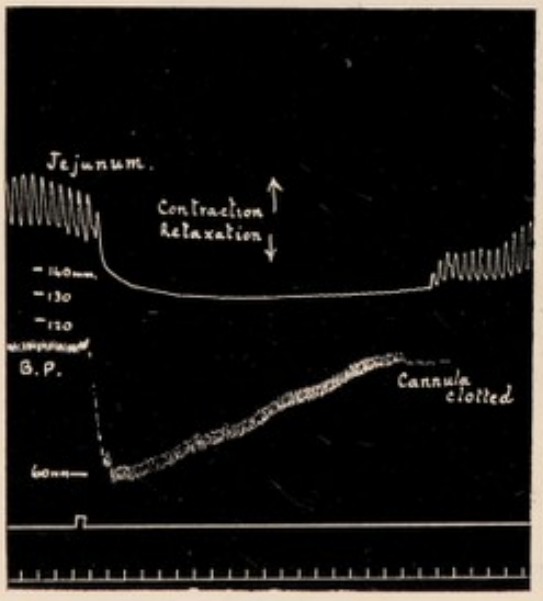

Fig. 11.

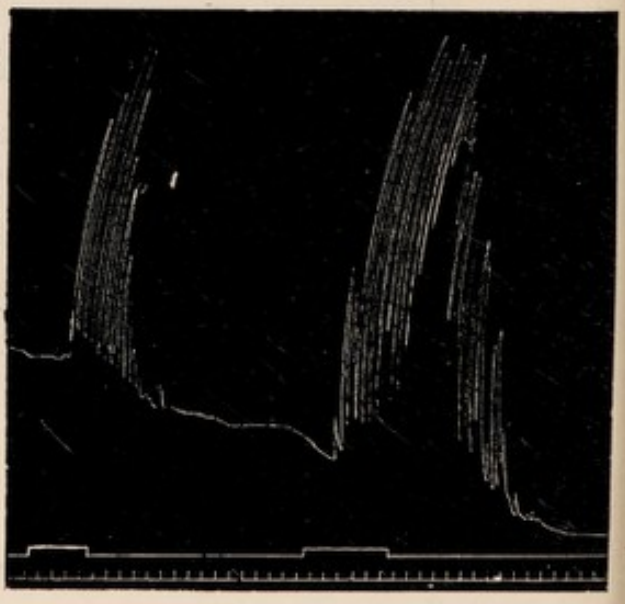

Fig. 12.

Fig. 11. $\times \frac{1}{2}$. Pithed cat. Blood-pressure and contractions of intestine (balloon and bellows record). Effect of 0·1 mgm. of adrenaline after 5 mgms. cornutine.

Fig. 12. $\times \frac{1}{2}$. Contractions of cat's jejunum (balloon and piston recorder) caused by 2 stimulations of the right vagus (coil at 8 cm.) after 150 mgms. chrysotoxin. Before the chrysotoxin was given the same stimulus was without visible effect.

effect of adrenaline on the jejunum of the cat at a stage when the effect on the blood-pressure was completely reversed. The inhibitory effect was apparently somewhat diminished in extent and duration, but it was always present with the weakest stimulation and with quite small doses of adrenaline. The same was true of the large intestine, as far as could be judged by direct inspection.

The effect of stimulating the cranial and sacral autonomic supplies was certainly not diminished. On the contrary, there was evidence that it was increased. Fig. 12 shows the effect on the jejunum of stimulating the vagus in the neck of an atropinised cat, after administration of 150 mgms. of chrysotoxin. The splanchnic nerves were intact, and previous stimulations of the vagus with the same strength of current had been without perceptible effect. It is impossible, in making such a comparison, to exclude altogether the "Bahnung" described by Bayliss and Starling[1] as the result of repeated excitation. But, in view of the difficulty of eliciting any response from the cat's intestine by vagus stimulation when the splanchnics are intact, some part in the very vigorous effect here shown may, with great probability, be attributed to the chrysotoxin. This may act by a relatively small depression of the sensitiveness of the sympathetic myoneural junctions, sufficient to weaken tonic inhibitory impulses from the spinal cord, but insufficient to make any considerable alteration in the powerful effect of adrenaline or electrical excitation of the splanchnics: or there may be an increase of excitability at some level of the cranial autonomic nerve-supply. The point of importance is that the motor myoneural junctions of the vagus are as little affected as its inhibitory endings in heart-muscle: and that the same is true of sacral autonomic endings is made obvious by the marked contraction of the large intestine still seen when the pelvic nerve is stimulated after large doses of chrysotoxin, sphacelotoxin, or cornutine.

4. The Intestinal Sphincters.

(1) *The ileo-colic sphincter.* Elliott[2] has shown that in many animals a short terminal portion of the circular muscle-coat of the small intestine is thickened to form an ileo-colic sphincter, which differs from the rest of the small intestine in giving a purely motor response to stimulation of the splanchnic nerves, to anæmia, or to adrenaline.

[1] Bayliss and Starling. This *Journal*, xxiv. p. 99. 1899.
[2] Elliott. This *Journal*, xxxi. p. 157. 1904.

My experiments were made on cats, anæsthetised with ether or with the brain pithed, the contractions of the sphincter being registered by Elliott's pencil-recorder and a small Brodie's bellows. A preliminary dose of adrenaline and stimulation of the splanchnics caused the normal contraction of the sphincter. Two successive doses of 50 mgms. each of chrysotoxin were then given intravenously. A few wave-like contractions of the sphincter were sometimes observed, but the main effect was a gradual loss of tone, so that, if the recorder was removed, the sphincter, as viewed from the opened large intestine, was seen to be widely relaxed. Neither large doses (1 mgm. or more) of adrenaline, nor stimulation of the splanchnic nerves, now caused any increase or diminution of the patency of the orifice, as observed directly or registered by the pencil-recorder. The efficiency of the apparatus to record a contraction was assured by gently pinching the sphincter, and its capacity for registering a further relaxation, if such had occurred, was shown by the fall of the lever when the recorder was displaced just above or below the grip of the sphincter. No trace of such relaxation was observed in the six experiments made, and it must be concluded that a mere extinction of the motor effect of the sympathetic nerves and of adrenaline is the result in this case of paralytic doses of ergot.

(2) *The internal anal sphincter.* Langley and Anderson[1] observed that the effect of stimulating the true sympathetic nerve-supply to this sphincter is motor in the cat, inhibitory in the rabbit. The uncertainty of the response in the rabbit and the motor effect obtained in the cat, led them to the view that there is an admixture of motor fibres in the sympathetic nerve-supply to the rabbit's sphincter: and on similar grounds the probability of an inhibitory admixture in the cat might be urged. My experiments were made on etherised or pithed cats, curare being given in addition to paralyse the external sphincter. The movements were observed either directly, the paralysed external sphincter being held open, or by the pencil-recorder method. Fig. 13 shows the motor effect of stimulating the hypogastric nerves before chrysotoxin was given. The administration of upwards of 100 mgms. of the latter caused only a loss of the tone of the sphincter. Stimulation of the hypogastric nerves then gave a purely inhibitory effect, illustrated in Fig. 14. The intravenous injection of adrenaline gave practically parallel results, the only divergence being that the motor response

[1] Langley and Anderson. This *Journal*, XVIII. p. 67. 1895.

before chrysotoxin was weaker, the inhibitory effect, after that drug was given, more marked and obtainable at an earlier stage of the paralysis than when the hypogastric nerves were electrically stimulated.

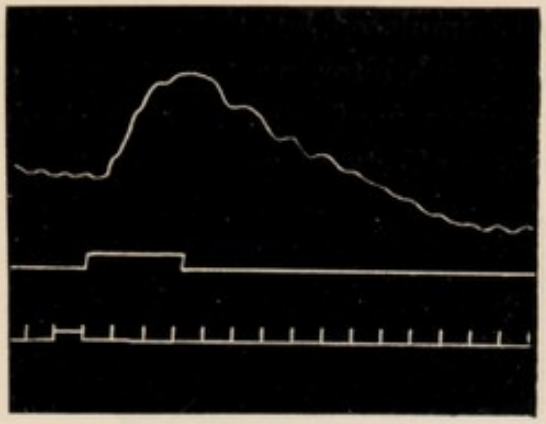

Fig. 13.

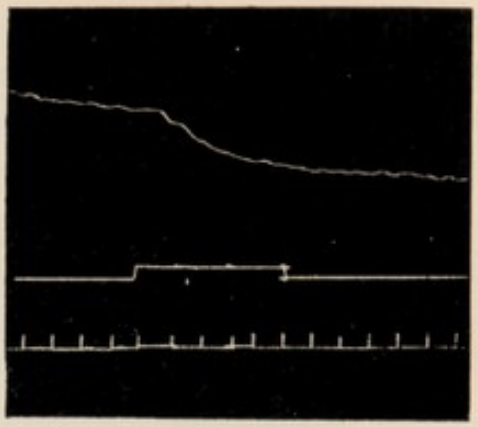

Fig. 14.

Fig. 13. $\times \frac{1}{3}$. Pencil-recorder and bellows record from internal anal sphincter of cat. Effect of stimulating both hypogastrics peripherally, coil at 10 cm. Contraction of sphincter. Adrenaline gave the same.

Fig. 14. $\times \frac{1}{3}$. Continuation of Fig. 13. Stimulation of hypogastrics with same current after 150 mgms. chrysotoxin. Relaxation of sphincter. Adrenaline caused similar relaxation. The lever was raised between Figs. 13 and 14: the tone of the sphincter in Fig. 14 was lower than in Fig. 13.

In the case of the two involuntary sphincters of the intestines of the cat we have, therefore, structures which both respond by contraction to stimulation of the sympathetic nerve-supply or to adrenaline. When the paralytic effect of ergot has been produced the same methods of stimulation produce in the one case no effect, in the other pure relaxation.

5. The Stomach.

The movements of the cat's stomach were recorded by passing a No. 12 silk catheter down the œsophagus and through the cardiac sphincter. The duodenum was tied just beyond the pylorus, the stomach filled with warm saline, and the œsophagus tied tightly round the catheter. The abdominal walls were opened and retracted, the whole abdomen being in a warm saline bath. The catheter was connected to a large bulb half-full of warm saline, which again communicated with a large bellows-recorder. A pithed cat was used. The injection of 50 mgms. of active chrysotoxin intravenously caused the normal rise of blood-pressure, which was accompanied by a slight increase in the tone and rhythm of the stomach. A second 50 mgms. produced no further

effect. Intravenous injection of 0·1 mgm. of adrenaline then caused a fall of tone and inhibition of rhythm practically identical with that which the same dose produced before administration of chrysotoxin: but in this case a slight fall of blood-pressure replaced the usual rise (Fig. 15). The splanchnics were not stimulated, but the result indicates sufficiently well that the sympathetic inhibitors to the stomach musculature are, like those of the intestines, unaffected by chrysotoxin in dosage sufficient to paralyse vaso-motor effects completely.

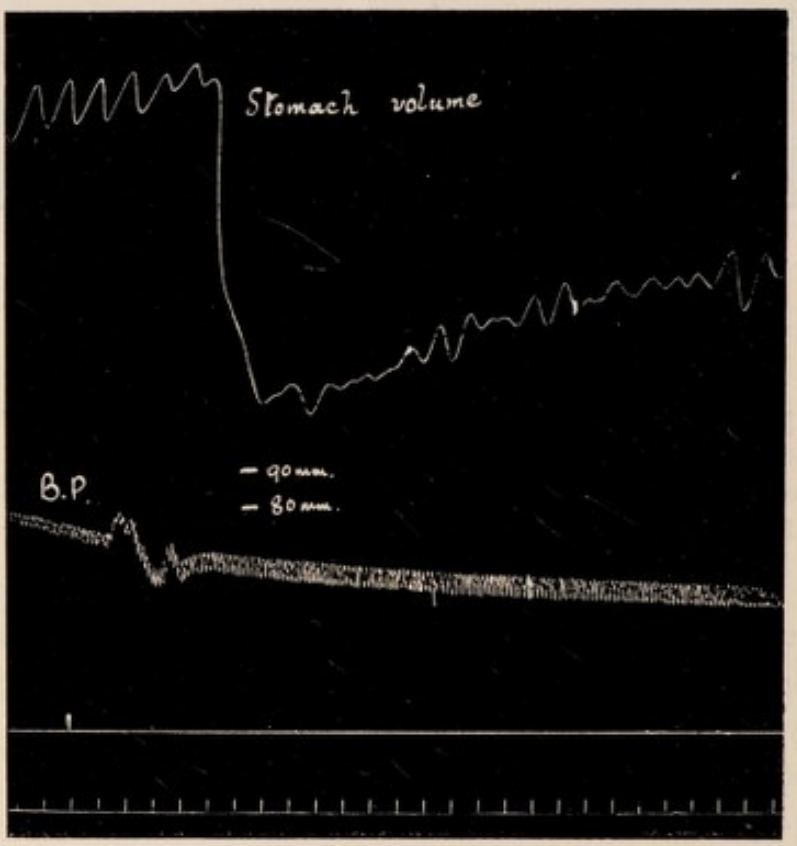

Fig. 15. ×¼. Stomach-volume (bellows-recorder) and blood-pressure of cat after 100 mgms. of chrysotoxin. Injection of 0·1 mgm. of adrenaline, causing relaxation of the stomach and slight fall of blood-pressure.

6. The Gall-bladder.

In a recently published paper by Bainbridge and myself[1] the effect of chrysotoxin on the gall-bladder of the dog was described. For details and figures reference to that paper may be made. Here it is sufficient to recall the fact that in the stimulant stage the drug caused some rise of tone and increase of rhythm, and that, when the paralytic effect was complete, adrenaline still caused perfect inhibition of

[1] This *Journal*, xxxiii. p. 138. 1905.

the gall-bladder without rise of blood-pressure; while it was only under these conditions that the motor effect of the vagus could be definitely and regularly observed. The effects are therefore closely similar to those on the small intestine of the dog and cat, the motor vagus and inhibitor true sympathetic nerve-supplies being alike immune from the paralysis.

7. The Urinary Bladder and Urethral Sphincter.

(1) *The cat.* The work of Langley and Anderson[1], Stewart[2], Lewandowsky[3], and Elliott[4], has shown that the effect on the bladder of stimulating the true sympathetic (hypogastric) nerves, or of adrenaline, is to cause contraction of the base of the bladder and of the urethral sphincter, relaxation of the fundus of the bladder itself.

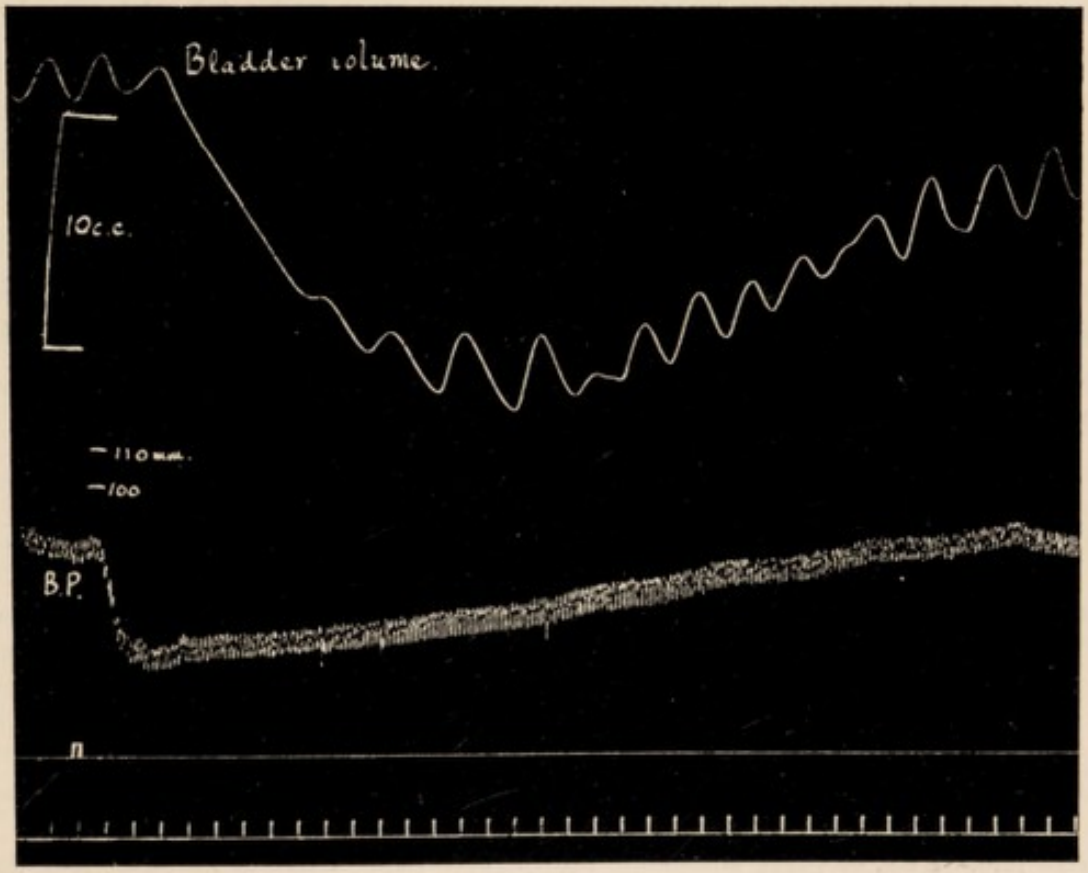

Fig. 16. × ½. Relaxation of bladder and fall of blood-pressure of cat caused by 0·5 mgm. adrenaline. Previously there had been injected 5 mgms. of a pure specimen of cornutine of which 1 mgm. caused vaso-motor reversal.

[1] This *Journal*, xix. p. 73. 1895.
[2] *American Journal of Physiology*, ii. p. 182. 1899.
[3] *Centralbl. f. Physiol.* xiv. p. 433. 1900.
[4] This *Journal*, xxxii. p. 401. 1905.

In my experiments the volume of the bladder contents was registered by the ordinary combination of catheter, water reservoir, and bellows-recorder. The level of the water in the reservoir was about 15 cm. above the fundus of the bladder. In the primary stimulant stage of their action ergot preparations cause a slight inhibition of the fundus succeeded by a prolonged, progressive increase of tone. This is not due merely to the rise of blood-pressure, since a second dose, which caused no further rise of blood-pressure, elicited a repetition of the bladder-response.

When the paralytic effect on the arteries was complete adrenaline still caused a full inhibition of the fundus, a dose of 0·2—0·3 mgm. causing 15 c.c. or more of water to enter the bladder from the reservoir: the relaxation was, moreover, of normal persistence (Fig. 16). The same result was obtained by direct stimulation of the hypogastric nerves: but the initial rise of the lever, normally observed with this method of stimulation, was now lost. Direct observation showed, however, that the contraction of muscle fibres over the base of the bladder was still present, though weak. Even after very large doses (200—300 mgms.) of chrysotoxin a feeble contraction was still perceptible.

The effect of adrenaline, and of stimulating the hypogastric nerves, on the urethral sphincter was tested by a method used by Elliott, the column of water supported by the sphincter being measured. The following extract from an experimental record illustrates the effect of chrysotoxin on the response of the sphincter to such stimulation.

Exp. 1. Female cat, weighing 3 kilograms.

10.30 a.m. Chloroform; then ether. Tracheotomy: vagi cut. Blood-pressure from carotid artery, cannula in external jugular vein.

11.5. Cannulæ in urethra: upper one, with connection to adjustable water column, tied into lower part of bladder: lower one inserted into meatus and not tied. About 15 mm. of urethra between the inner orifices of cannulæ. Upper cannula clamped in position. Hypogastric nerves decentralised and peripheral ends put on Ludwig electrodes.

11.50. Drops issue from lower urethral cannula when pressure reaches 16 cm. water: cease when pressure falls to 14 cm.

12.25 p.m. 2 c.c. of $\frac{1}{100000}$ adrenaline into jugular vein. Urethral sphincter now does not open till pressure reaches 34 cm.

1.25. Urethral sphincter opens at 17 cm. pressure, closes again at 16 cm.

1.38. Stimulation of hypogastric nerves, coil at 8 cm. Contraction of base of bladder raised water-column to 24 cm. Urethral sphincter resisted this, and did not open till pressure was raised to 34 cm.

1.40. 50 mgms. sodium chrysotoxin in 5 c.c. of water injected into jugular vein. B-p. rises from 96—120 mm. and then falls to 46 mm. as respiration fails. Artificial respiration applied. Urethral sphincter relaxes, opening now with

pressure of 11 cm. water. Remnant of bladder exhibits rhythmical contractions, causing spirts of fluid through relaxed urethra.

1.49. 50 mgms. sodium chrysotoxin. B-p. rises from 56—72 mm. and falls again to 56 mm. Urethral sphincter now opens at 10 cm. water.

1.55. Stimulate hypogastrics: coil at 8 cm. Base of bladder contracts slightly, raising pressure to 12 cm., at which pressure water escapes through urethra, and continues to do so until pressure falls to 9 cm. There is obviously no contraction of the sphincter.

2.9. Stimulate hypogastrics. Coil at 7·5. No contraction of urethral sphincter, which again opens at 9 cm.

2.13. 2 c.c. $\frac{1}{10000}$ adrenaline by jugular vein. B-p. falls from 90 mm. to 76 mm., remains depressed for 1 min. and then rises to reach 100 mm., 2 min. from injection. Urethral sphincter unaffected, opening at 10 cm.

2.18. Stimulation of hypogastrics, coil at 4 cm. No effect. Urethra becomes pervious at 10 cm. pressure.

2.23. 5 c.c. $\frac{1}{10000}$ adrenaline by the jugular vein. B-p. rises from 68—94 mm., the rise being apparently due to augmentation and acceleration of the heart-beat. Urethra unaffected, being pervious at 8 cm. pressure.

It is clear that ergot in large doses annuls the motor response of the urethral sphincter to stimulation of the hypogastric nerves and to adrenaline. To stimulation of the pelvic nerves, or of the sacral roots, the bladder responds after ergot, as before, by complete and sustained contraction.

(2) *The ferret.* The experiment was performed at Cambridge by Mr T. R. Elliott, and a full description of the result is given in his paper on the action of adrenaline[1]. We found that the motor effect of the hypogastric nerves and of adrenaline on the fundus of the bladder was changed, by 30 mgms. of chrysotoxin, into a purely inhibitor response to adrenaline, and a predominant inhibition with preliminary motor phase with stimulation of the hypogastrics. The motor effect evoked by electrical excitation of the nerves was, therefore, as in other cases, more resistant to the paralysis than that of adrenaline. Nicotine still caused the usual contraction, showing that the motor supply by the pelvic nerves was, as elsewhere, not paralysed.

8. The Pilo-motor Muscles.

In my preliminary account it was stated that the pilo-motor effect of stimulating sympathetic nerves was not affected by chrysotoxin. The statement was made on the basis of an observation made at the end of an experiment, about an hour after a sufficient dose of chrysotoxin had been administered to reverse the effect of adrenaline on the blood-

[1] This *Journal*, xxxii. p. 401. 1905.

pressure. Later experience having shown that the effect of any but a very large dose of the drug would after an hour be diminishing, and that other sympathetic motor supplies, such as that to the base of the bladder, need larger doses for the production of the paralysis than such as suffice for the vaso-motor reversal, the experiment has been twice repeated. The result has shown that a large dose, such as 200 mgms. or more of chrysotoxin, is sufficient to annul the pilo-motor effect, or, at least, to reduce it below the limit of perception. A protocol of one experiment may be given in illustration.

Exp. 2. Male cat weighing 3 kilograms.

11.50 a.m. Chloroform: brain pithed, tracheotomy, artificial respiration. Blood-pressure from carotid artery; cannula in external jugular vein. Vagi cut.
Abdomen opened, sympathetic cords exposed and ligatured just below 4th lumbar ganglia. Ludwig electrodes on cords between ligature and 5th lumbar ganglia.

12.24. p.m. Stimulation of sympathetic cords. Coil at 12 cm. Rapid and marked erection of hairs on the dorsum and sides of the tail.

12.30. Injection of 100 mgms. chrysotoxin dissolved by the aid of NaOH in 10 c.c. of water.

12.40. Injection of another 100 mgms. chrysotoxin.

12.50. Stimulate sympathetic cord, coil at 12 cm. No erection of hairs visible.

12.52. Stimulate, coil at 10 cm. No effect. Coil pushed to 8, 6, 4, 2 cm., and finally pushed home, stimulation being repeated in each position. No trace of pilo-motor effect could be detected. With the last 3 stimulations escape of current caused tetanic contractions of muscles of back and legs.

1.4. Sympathetic cords freed between 5th and 6th lumbar ganglia; electrodes transferred to this position and held up to prevent current escape. Stimulation repeated, with coil at 12, 10, 8, 6, 4, 2 cm. and pushed home. No trace of pilo-motor effect observable.

9. The Plain Muscle of the Eye.

Stimulant effects. The following is the train of phenomena observed when 50 mgms. of chrysotoxin, or 1—2 mgms of "sphacelotoxin" or "cornutine," is injected intravenously.

(1) Brief dilation of the pupil, lasting a few seconds only. This is unaffected by section of the cervical sympathetic nerve, but is absent after removal of the superior cervical ganglion.

(2) Steady contraction of the pupil, accompanied by retraction of the nictitating membrane, opening of the palpebral fissure, and slight protrusion of the eyeball. The process is slow and may take 10 minutes or more to become complete. A second dose of the drug accelerates and intensifies the constriction. When it is complete the eye presents the appearance shown in Fig. 17 (right eye). Section of the third nerve

intracranially[1] makes the constriction a little slower; but 20 mgms. of atropine intravenously does not abolish it or prevent it.

Fig. 17. $\times \frac{1}{2}$. Effect on pupil of 100 mgms. of chrysotoxin. The effect was complete about 10 minutes after injection. The left carotid was tied, and the effect appeared in the left eye later and very slowly.

Paralytic stage. By giving very large doses of ergot preparations I have succeeded in abolishing completely the dilator effect on the pupil of the largest doses of adrenaline tried (up to 5 mgms.). Strong electrical stimulation of the cervical sympathetic nerve, however, always produced a slight remnant of dilator effect. In one instance the pupil gave, before chrysotoxin was injected, a maximal dilation when the nerve was stimulated with the coil at 30 cm. After 250 mgms. of chrysotoxin had been given the coil had to be pushed up to 5 cm. before any reaction was observed. In several other similar experiments the first sign of reaction was obtained with the coil at 10 cm. In no case is the reaction so obtained a normal dilation. The pupil widens slowly into an ellipse and finally into a small circle. When the stimulation is stopped it remains in this semi-dilated condition for 10 secs. or more and then slowly constricts to a slit again. The intense tone of the sphincter is doubtless responsible for this abnormal type of dilation: the abolition of the dilator effect of adrenaline and the strong stimulus needed to elicit a response through the cervical sympathetic must, on the other hand, be taken as evidence of incomplete paralysis of the sympathetic myoneural junctions.

10. The Uterus.

The reaction of this organ was examined in the cat, the rabbit, and the monkey. Contractions of the uterus and vagina were usually recorded together, since it was found that they contracted as one. In the cat records were made of the contractions of the non-pregnant uterus and of the uterus in the early stages of pregnancy, by attaching

[1] The experiment was very kindly performed for me at Cambridge by Dr H. K. Anderson.

a thread to both horns at a point about $\frac{2}{3}$ of their length from the cervix. The longitudinal pull of combined uterus and vagina was then recorded, either by passing the thread over pulleys to a lever, which was drawn down by contractions, or by attaching the thread to the short, counterpoised lever of Brodie's bellows, which was connected by rubber tubing to a second recording bellows, the lever in this case moving upwards with contractions. The cat was pithed and given a small dose of curare in addition to eliminate twitching of the perineal muscles.

An experiment with a pencil recorder in the vagina having demonstrated that the reaction of circularly disposed fibres followed the same course as that of the longitudinal ones the method was not used again. In one cat it was possible to insert a balloon into one horn of the uterus. Details of this experiment are given below.

In the non-pregnant rabbit the thread and pulley method of

Fig. 18.

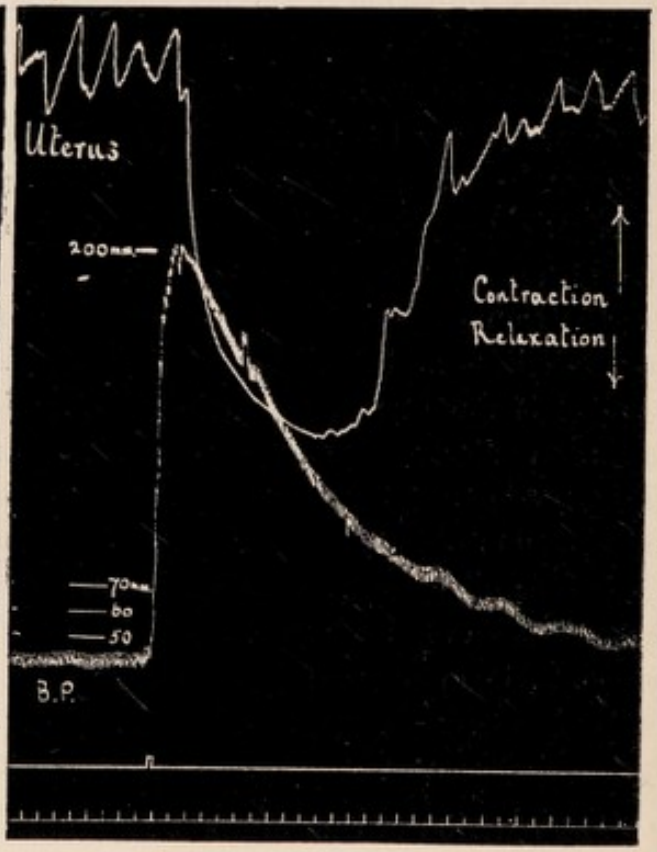

Fig. 19.

Fig. 18. $\times \frac{1}{2}$. Contraction of rabbit's uterus and vagina (non-pregnant) produced by 0·1 mgm. adrenaline.

Fig. 19. $\times \frac{1}{3}$. Rise of blood-pressure and relaxation of uterus of non-pregnant cat caused by injection of 0·1 mgm. adrenaline. Double-bellows record. Stimulation of hypogastrics gave similar effect.

recording was used, as also in the monkey, in which animal the thread was attached to the fundus of the uterus.

It is necessary, in the first place, to describe the effects on the uterus of stimulating the sympathetic nerve-supply and of giving adrenaline in the three types used, as they are observable with the help of graphic records. In the rabbit the motor effect, as described by Langley and Anderson[1], is so evident that the graphic record is quite unnecessary for its detection, and Fig. 18 is merely given for comparison with the record obtained after chrysotoxin. Direct observation, moreover, alone detects the pallor of the uterus accompanying the contraction produced by adrenaline or by stimulation of the hypogastric nerves.

It is otherwise in the cat. Langley and Anderson[2] described the marked pallor of the uterus caused by stimulating the sympathetic nerves, and observed that the motor effect was much less pronounced and constant than in the rabbit. Langley[3] observed the same effect with adrenaline. The graphic record shows that, in the non-pregnant cat, with either method of stimulation, the motor effect, if present at all, is a trifling preliminary phase, giving way to the main, and frequently the only effect, which is a pronounced inhibition both of tone and rhythmic contractions (Fig. 19). The experiment has now been made a large number of times and the result has always been the same, in the virgin as well as the non-pregnant, multiparous cat.

A remarkable difference of reaction appears when the cat's uterus is examined in the early stages of pregnancy[4]. Two experiments were made on cats in which each horn of the uterus contained several ova, each measuring about 2 cm. in diameter. The recording method used for the non-pregnant organ served quite well for this condition also, the thread being attached to symmetrical points between the ova. The effect of adrenaline and of stimulating the hypogastric nerves was, in both these cases, purely motor, the vagina shortening visibly and the horns of the uterus being both shortened and contorted. Fig. 20 shows the record of such a contraction.

On cats in the later stages of pregnancy I have made two experiments: but the recording method was not suited to the conditions, and

[1] This *Journal*, XIX. p. 122. 1895. Langley. This *Journal*, XXVII. p. 252. 1901.

[2] *loc. cit.* [3] *loc. cit.*

[4] This change of the response of the cat's uterus with functional conditions has, since this account was written, been independently observed by Prof. Cushny, and was demonstrated by him to the Physiological Society on March 24th.

further experiments on the reaction at this stage is needed. The effect of adrenaline, as shown by the record, was, in one case, contraction followed by inhibition, in the other pure contraction. The hypogastric nerves could not conveniently be reached for stimulation under the conditions of the experiment.

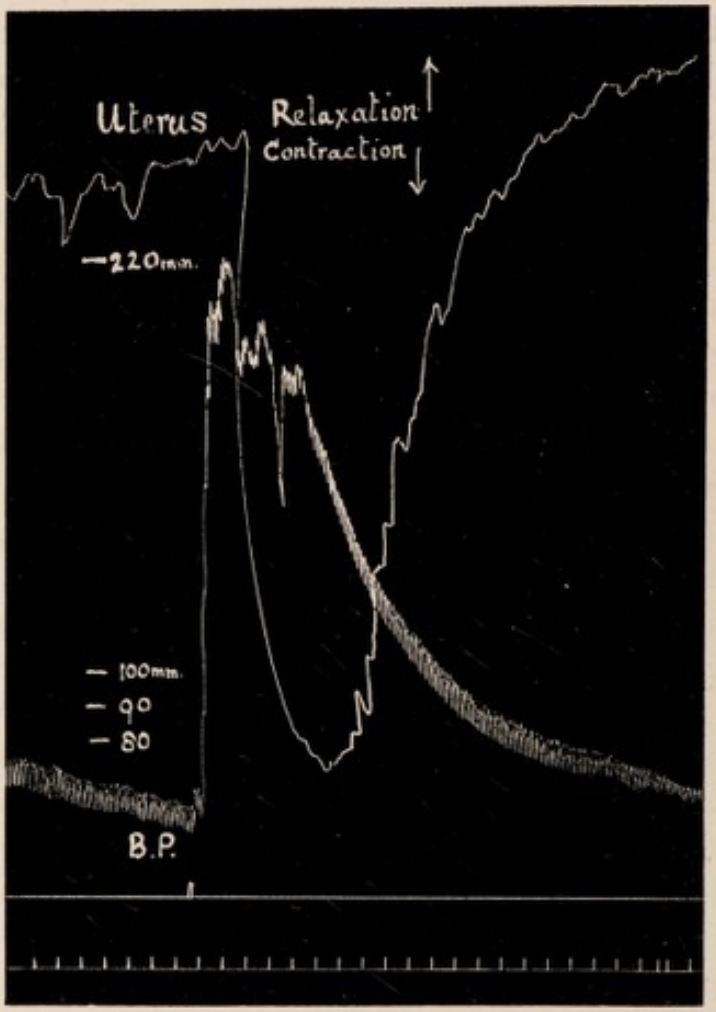

Fig. 20. × ⅓. Contraction of early-pregnant uterus of cat caused by 0·1 mgm. adrenaline. String and pulley record. Note that lever moves opposite way to that of Fig. 19. Stimulation of hypogastrics gave similar effect.

One experiment was made on a cat which had, apparently, given birth recently to young, the involution of the uterus being defective. Both uterus and vagina were large, soft and doughy, and it was quite easy to pass a balloon attached to a catheter up the vagina into the uterine cavity. This was distended with water and connected to a water reservoir and bellows recorder. The distension of the balloon caused a gradually increasing tone of both horns and body of the uterus. The bellows record also showed rhythmic contractions. Intravenous injection

of 0·1 milligram of adrenaline caused pure inhibition of both tone and rhythm.

In the experiment on the monkey the uterus gave a weak motor reaction to adrenaline. The animal was a young virgin and the uterus accordingly very small.

Stimulant effects of preparations from ergot. Kobert[1] stated that sphacelinic acid caused the condition known as "tetanus uteri," cornutine causing rhythmic contractions. Jacobj[2] using pregnant cats, described

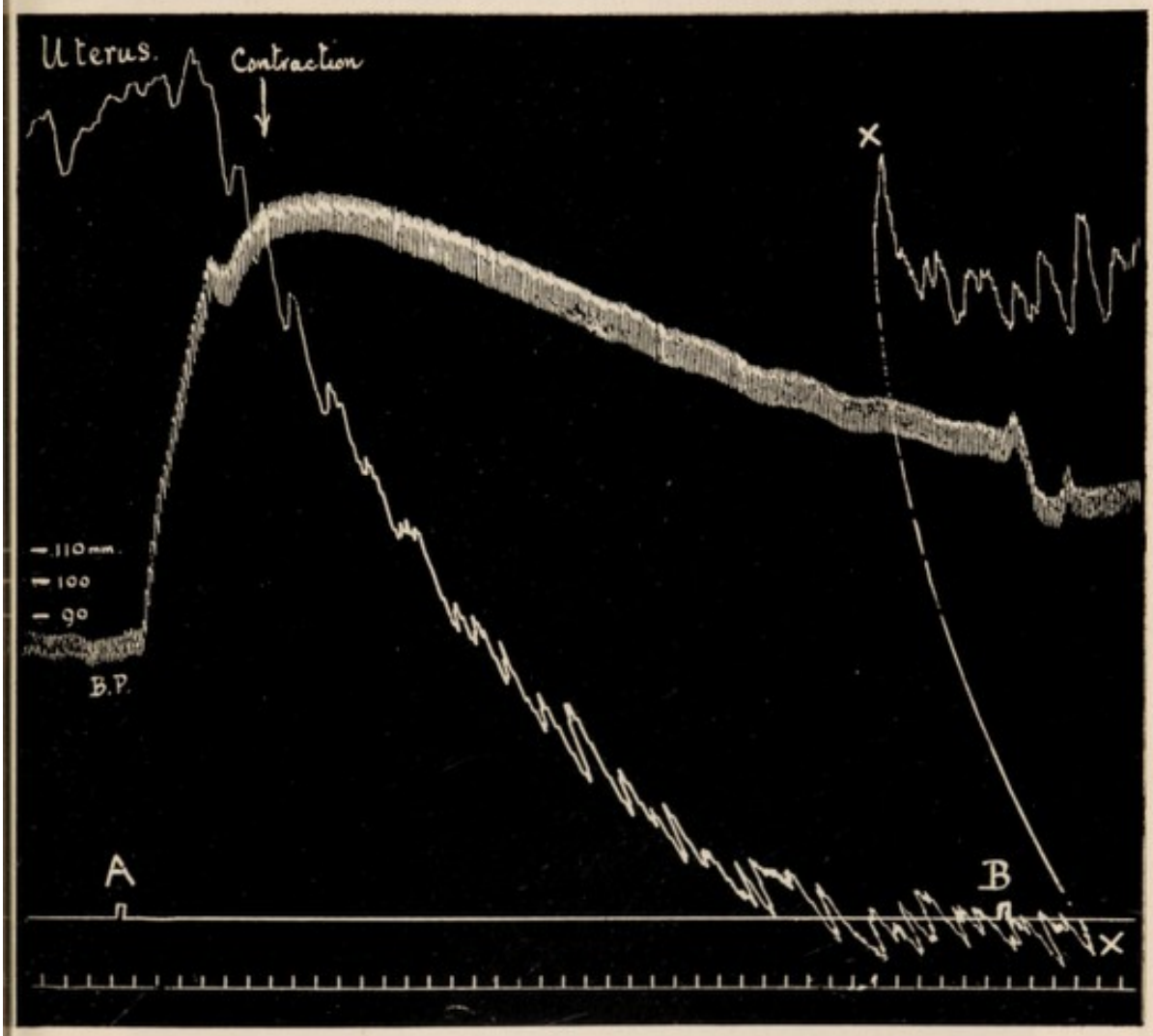

Fig. 21. × ⅓. From same experiment as Fig. 20. Injection of 2 successive doses each of 10 mgms. impure cornutine (equivalent to about 1 mgm. dose of the purest specimen yet obtained). First, *A* produces large rise of blood-pressure and very pronounced contraction of uterus. As the lever was being pulled off the drum it was raised, by adjustment of pulleys, between *X*—*X*. At *B*, the second injection of 10 mgms., caused slight fall of blood-pressure and did not perceptibly affect the tone or rhythm of the uterus.

[1] *loc. cit.* [2] *loc. cit.*

rhythmic waves of contraction as the effect of injecting chrysotoxin intravenously.

Kurdimowsky[1] observed contraction of the isolated uterus of the rabbit when sphacelinic acid was added to the perfusion-fluid; but stated that the contraction was much less marked than that produced by adrenaline. He described the reaction as tetanic in nature.

In the non-pregnant rabbit the effects I have obtained have been inconstant, and usually weak, a slight augmentation of the natural rhythm of the uterus being the only effect observed. Chrysotoxin was the preparation used. In one pregnant rabbit, marked, rhythmically repeated contractions of the uterus, vagina, and plain muscle of the broad ligaments resulted from the injection of 50 mgms. of chrysotoxin.

In the cat the effect, like that on the blood-pressure, is much more vigorous than that seen in the rabbit. Even in the non-pregnant uterus, giving a predominantly inhibitory response to stimulation of the sympathetic nerve-supply and to adrenaline, a marked motor reaction is elicited by 50 mgms. of active chrysotoxin, or by 1—5 mgms. of "sphacelotoxin" or "cornutine." The nature of the reaction was in all cases the same, namely a considerable development of tone, and some

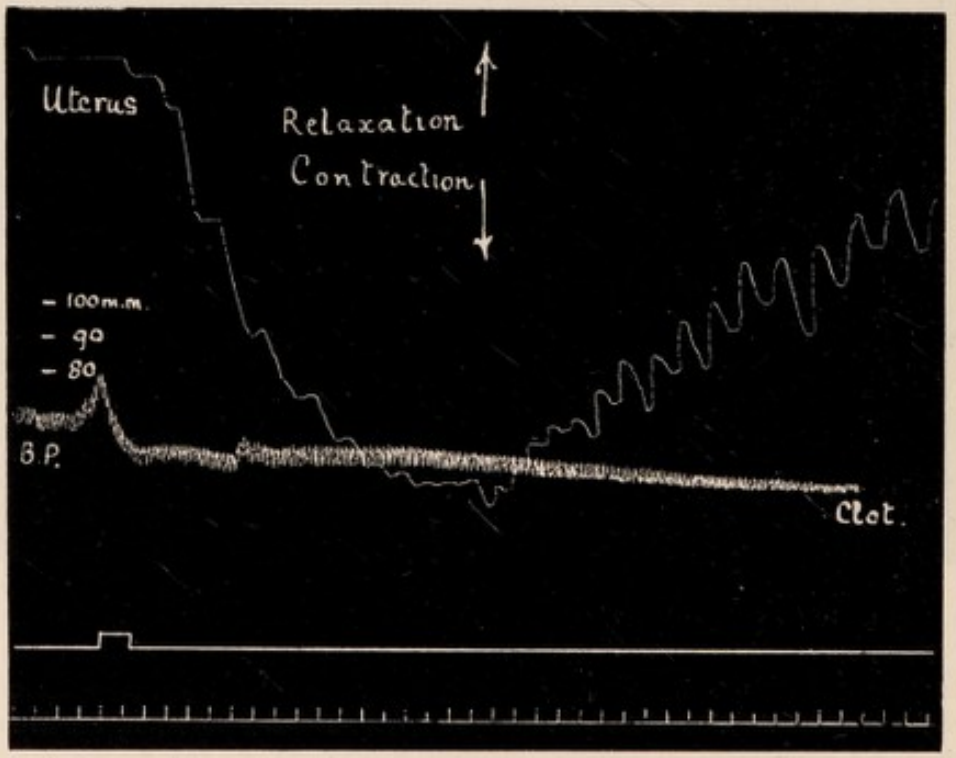

Fig. 22. × ⅓. Contraction of monkey's uterus (young virgin) produced by injection of 50 mgms. chrysotoxin. Blood-pressure slightly depressed.

[1] *Arch. f. Gynaekologie*, LXXIII. p. 425. 1904.

increase in the amplitude of the rhythmic contractions. The same type of reaction was given in an even more striking manner by the uterus in early pregnancy (see Fig. 21). The effect is a prolonged one, and persisted in some degree throughout the experiment. In some cases the augmented tone and rhythm showed a periodic diminution and revival. Some pallor of the uterus, but less than that produced by adrenaline, was observed. In the monkey (young virgin) the effect was similar. The first injection (50 mgms. of chrysotoxin) caused increase of tone and appearance of rhythm in the previously inactive uterus (Fig. 22). Both effects passed off rather quickly, and a second injection, given as soon as the effect of the first had practically disappeared, caused only a temporary revival of the rhythm. Since in the monkey the drug hardly affected the blood-pressure the effect on the uterus must be a primary one. In the cat, too, there is no distinct relation between the two sets of effects: some cats, in which the blood-pressure effect was comparatively small, showed marked uterine effects, and *vice versâ*. Probably, therefore, vascular changes are but little, if at all, concerned in the production of the increased uterine activity.

Without entering here into the chemical aspect of the question, attention may be drawn to the fact that no difference in the form of uterine stimulation was observed between the preparations which, being made from chrysotoxin by Jacobj's method, I called "sphacelotoxin," and those which were obtained from ergot by the methods which, according to Kobert, yield "cornutine." In both cases increase of tone and exaggeration of rhythm were produced.

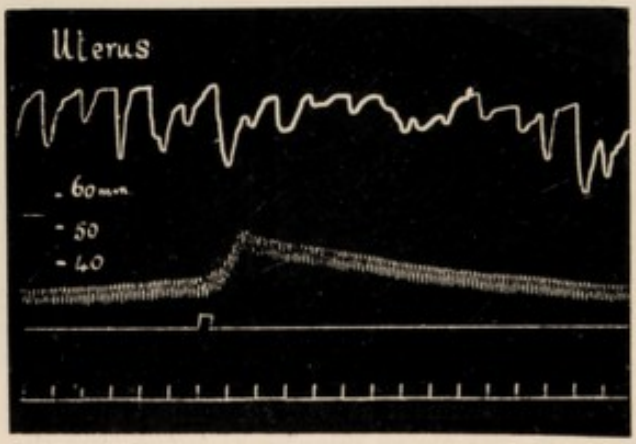

Fig. 23. × ½. Blood-pressure and uterine contractions of rabbit. Same experiment as Fig. 18. After 200 mgms. chrysotoxin 0·1 mgm. adrenaline was again given, producing the effect shown—slight inhibition of uterine rhythm, and practically no rise of blood-pressure.

Paralytic effects. On the uterus, as on the other tissues innervated by nerves of the true sympathetic system, all the preparations used produce, in large doses, the characteristic change in the response to adrenaline or stimulation of the sympathetic nerves. Under these conditions the uterus of none of the types examined gives any motor response to such stimuli. Fig. 23 shows the effect on the rabbit's uterus of adrenaline after 200 mgms. of chrysotoxin had been given: the response of the same uterus before chrysotoxin was shown in Fig. 18. It will be seen that the effect of adrenaline after chrysotoxin (Fig. 23) is a slight, but perceptible inhibition of the rhythmic contractions.

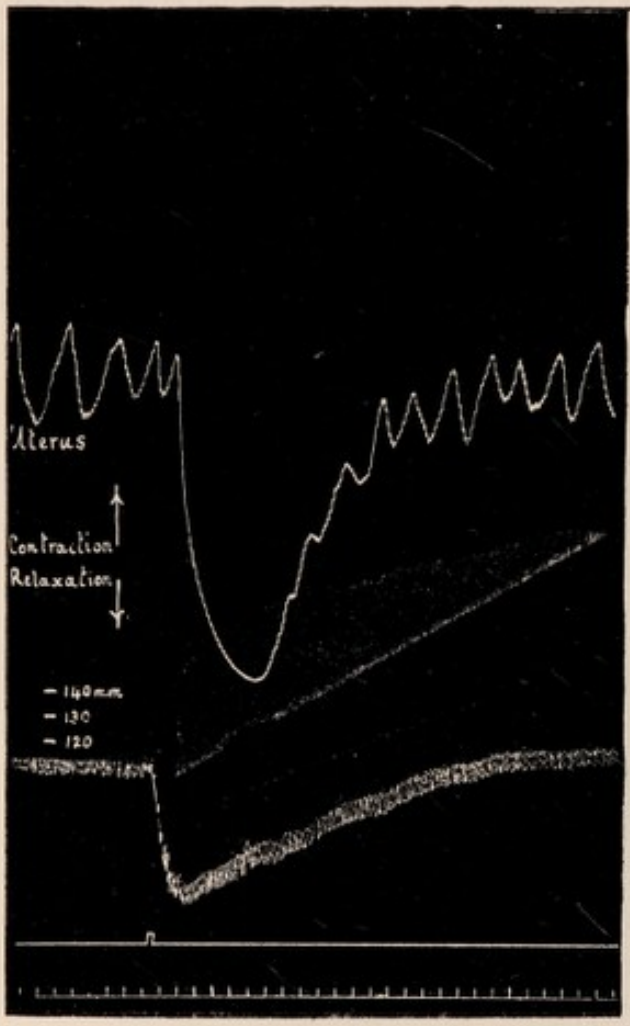

Fig. 24.

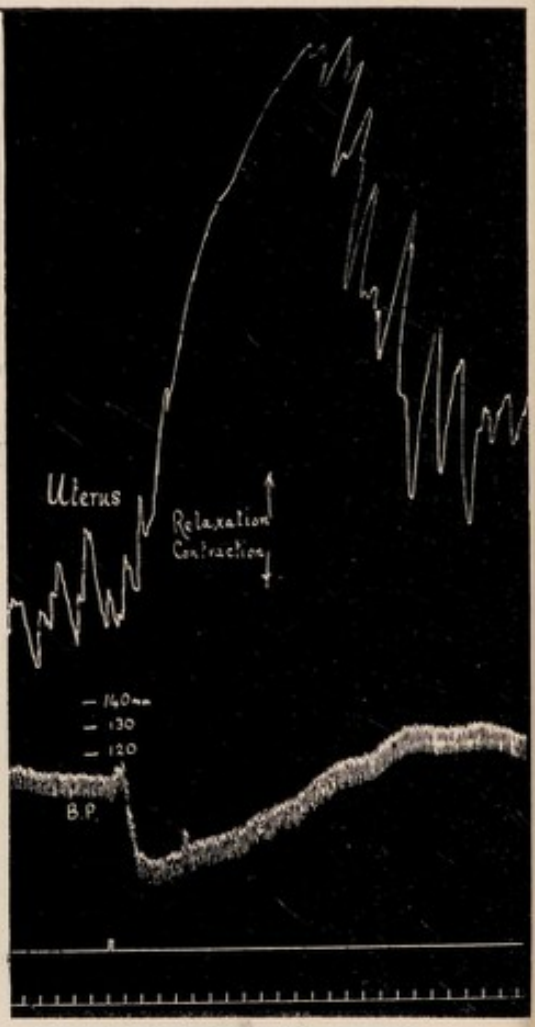

Fig. 25.

Fig. 24. $\times \frac{1}{2}$. From same experiment as Fig. 19. Effect of 0·1 mgm. adrenaline after 100 mgms. chrysotoxin, the uterus relaxing as before, but the blood-pressure now falling.

Fig. 25. $\times \frac{1}{2}$. From same experiment as Fig. 20. Fall of blood-pressure and relaxation of uterus of pregnant cat produced by 0·1 mgm. adrenaline after 20 mgms. impure cornutine.

In the cat, whether the normal effect is inhibitor, motor, or diphasic, the effect, after ergot, is pure inhibition of tone and rhythm. Figs. 24 and 25 are taken from the same two experiments as Figs. 19 and 20. It will be seen that the non-pregnant uterus, giving the inhibitor response shown in Fig. 19, preserves its reaction to adrenaline practically unaltered (Fig. 24) after a dose of chrysotoxin sufficient to cause a reversal of the normal blood-pressure effect. On the other hand, the early-pregnant organ, which contracted strongly with adrenaline (Fig. 20), relaxed as obviously when adrenaline was given again after 10 mgms. of impure "cornutine" (Fig. 25). Direct observation of the cat's uterus during such experiments reveals the fact that, whereas it normally becomes intensely pale when adrenaline is given or the hypogastrics stimulated, whether the intrinsic uterine muscle contracts

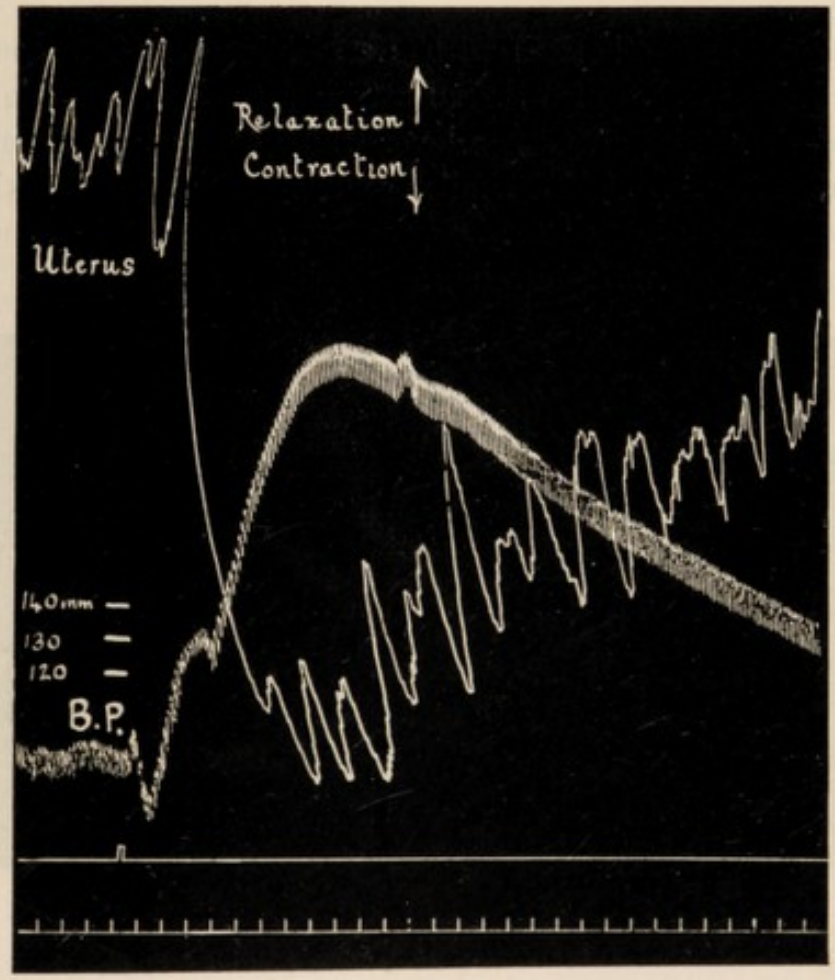

Fig. 26. $\times \frac{1}{3}$. Continuation of experiment illustrated in Figs. 20 and 25. After the effect shown in Fig. 25, extract from 0·4 gram. dried ox-pituitary was given intravenously, producing the rise of blood-pressure and contraction of the uterus shown in the figure.

or relaxes, after large doses of ergot the relaxation produced by either mode of stimulation is accompanied by a slight, but distinct flushing of the organ.

In the monkey the inhibition of the uterus produced by adrenaline after ergot affects both tone and rhythm and there is an after-effect, in the shape of a great exaggeration of the rhythm, which is possibly attributable to hyperæmia. The same phenomena are seen, though less marked in the cat.

As in the case of the blood vessels, the power of the uterine muscle still to respond by normal contraction to an appropriate stimulus, when the sympathetic motor effect has been completely annulled by ergot, is easily demonstrated by giving pituitary extract intravenously (Fig. 26).

11. Retractor Penis. (Dog.)

The dog was anæsthetised with A.C.E. mixture. The contractions were recorded by means of a thread attached to the tip of the retractor and passing over two pulleys to a lever which was pulled downwards by contraction of the muscle. A similar connection was made with another lever, by a thread attached to the prepuce, as a control on movements of the whole penis with respiration.

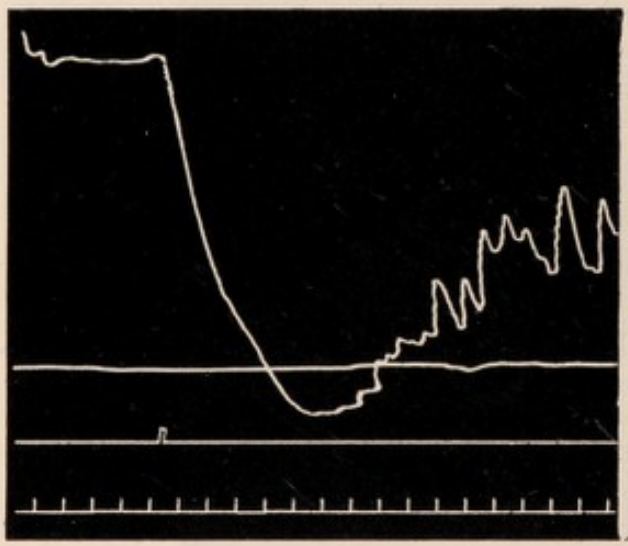

Fig. 27.

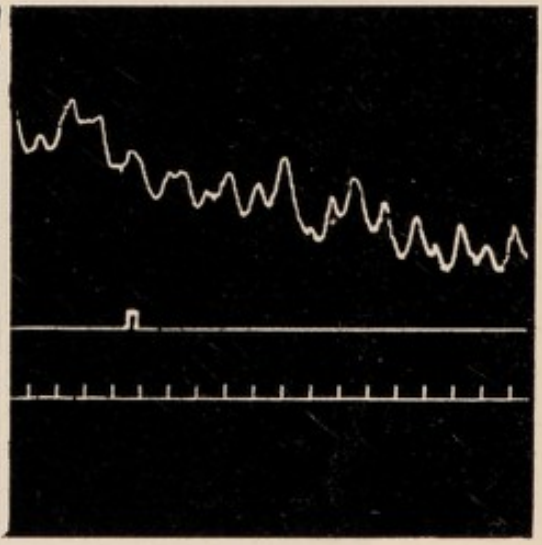

Fig. 28.

Fig. 27. $\times \frac{1}{3}$. Contraction of retractor penis of dog produced by injection of 0·1 mgm. adrenaline intravenously. Usual rise of blood-pressure. Second line of tracing = control lever from prepuce.

Fig. 28. $\times \frac{1}{3}$. Same experiment as Fig. 27, after injection of 200 mgms. chrysotoxin. 0·1 mgm. of adrenaline again injected, producing, as shown, no effect on retractor penis. Slight fall of blood-pressure occurred.

The usual motor reaction was obtained by stimulating the pudic nerves and giving adrenaline intravenously (Fig. 27), the usual rise of blood-pressure accompanying the latter mode of stimulation. Chrysotoxin was then given, 200 mgms. being, in all, injected. The primary effect was a small increase in the tone of the retractor and the amplitude of its rhythmic contractions. Subsequent injections of adrenaline and stimulation of the pudic nerve had no perceptible influence, in either direction, on the activity of the retractor (Fig. 28).

12. The Submaxillary Gland.

The experiments were made on cats with the brain pithed. The results were uniform, and are illustrated by the following experimental record:

Exp. 3. Male cat, weighing 2870 grms.

10.45 a.m. Chloroform. Cerebrum pithed. Tracheotomy. Artificial respiration. Vagi cut. Cannula in Wharton's duct.

11.22. Chorda tympani stimulated to fill cannula, which was then connected to a long, narrow, slightly inclined tube. Each cm. of scale = 0·04 c.c. Cervical sympathetic isolated for stimulation.

11.27. Cervical sympathetic stimulated: coil at 10 cm. Column moved 4 cm. in 30 secs.

11.33. Chorda tympani stimulated: coil at 10 cm. Column moved 6·8 cm. in 30 secs. Cannulæ in right femoral artery and left femoral vein.

11.47. 2 c.c. $\frac{1}{10000}$ adrenaline into femoral vein. Column starts at 2·0 cm. No movement for 15 secs., then readings of 15 secs. intervals:—4·0, 5·0, 6·2, 7·3, 8·4, 9·4, 10·3, 11·1, 11·9, 12·2, 12·5, 12·8, 12·9, 12·95, stopped.

11.55. Column let down to 3·5. Stim. cervical sympathetic coil at 10 cm. Readings at 15 secs. intervals from beginning of stimulus:—5·3, 6·1, 7·3, 8·1, 8·4, 8·8.

11.58. 10 mgms. impure cornutine into femoral vein. No secretion, position of column remaining steady.

12.2 p.m. 2 c.c. $\frac{1}{10000}$ adrenaline. *No secretion.* B-p. rose from 70 mm. to 100 mm. (Heart-beat strengthened.)

12.5. 1 c.c. $\frac{1}{10000}$ adrenaline. B-p. fell from 100 mm. to 90 mm. *No secretion.*

12.6. Chorda tympani stimulated: coil at 10 cm. Readings at 15 secs. intervals. Started at 8·6: 10·5, 12·6, 14·2, 15·4, 16·1. Stimulation stopped.

12.10. Cervical sympathetic stimulated: coil at 10 cm. Pupil dilates. *No secretion.*

12.12. Chorda tympani stimulated: coil at 10 cm. Readings at 15 secs. intervals. Start at 6: 7·7, 8·7, 10·3, 11·5, 12. Stimulation stopped. Secretion continued for 15 secs. longer.

It is clear that the secretory effect of stimulating the sympathetic nerve-supply and of injecting adrenaline are quite annulled, while the chorda tympani retains its function unimpaired.

Discussion of the foregoing results.

Among the primary, or stimulant effects of the preparations from ergot used in these experiments one only admits of simple and immediate analysis. The constriction of the pupil, being unaffected by large doses of atropine, must be attributed to a stimulus acting peripherally to the structures which atropine paralyses, that is, on the muscle fibres themselves. It seems probable that the motor effects on the bladder and bowel, in so far as they are primary effects of the drug's action, will prove to be of a similar nature. But in regard to the effects of chief practical interest, those on the arteries and the uterus, it is impossible at present to come to a conclusion. Perfusion experiments have given inconsistent results in the hands of different experimenters. Jacobj[1], with sphacelotoxin, observed constriction of the limb-vessels of a dog. On the other hand Kurdinowsky[2], with sphacelinic acid, found the vessels of the isolated uterus unaffected; and Dixon[3] has recently stated that addition of ergot to a perfusion fluid causes vaso-dilation. A difference of animals and preparations doubtless contributes to the discrepancy. Kurdinowsky used rabbits, in which vaso-constriction by ergot is not, in my experience, to be expected under any conditions: and Dixon used extracts containing much beside specific active principles. In any case the question cannot be regarded as settled by these experiments in favour of or against peripheral action. Nor do experiments made by recording the blood-pressure lead to a definite conclusion. One point is easily ascertained. The rise of blood-pressure occurs quite normally in a cat in which the spinal cord is completely destroyed, so that the phenomenon is not of central origin. On the other hand nicotine and apocodëine (30 mgms. and 100 mgms. respectively for a cat) reduce it to a minimum, or abolish it completely. This last fact suggests the cells of the sympathetic ganglia as the seat of the stimulus: but it is necessary to bear in mind the concomitant paralytic effect of ergot on the sympathetic myoneural junctions, which cannot but complicate the results of such an experiment. On the whole, therefore, it seems advisable to postpone definite opinion as to the nature of these stimulant effects on the arteries and the uterus. If the paralytic effects are caused by a different substance, and if it should prove possible to separate a purely stimulant principle, the solution of the question will at once become easier.

[1] *loc. cit.* [2] *loc. cit.*

[3] Dixon. *Lancet*, 1906 (March—June), p. 827.

In the case of the paralytic action an analysis of the observations now available for discussion leads to a much more definite result. It has been shown already that the reversal of the vaso-motor action of adrenaline and of sympathetic nerves, which formed the starting-point of this investigation, is due to an action on those structures which adrenaline stimulates. We have now the further information that these are the only structures in the peripheral nervous and muscular systems which the paralysis affects. Stimulation of the vagus still inhibits the heart-beat and provokes contractions of the stomach, intestine and gall-bladder: stimulation of the chorda tympani evokes the usual secretion from the submaxillary gland: stimulation of the pelvic nerves or the sacral roots excites contractions of normal vigour in the bladder and the large intestine, and dilation of the vessels of the penis. All these effects are quite undiminished by doses of ergot far larger than those necessary to produce the reversal of the vaso-motor and other effects of the true sympathetic nerves. The same is true of the contraction of skeletal muscle fibres in response to excitation of motor nerves. The junctions of preganglionic fibres with ganglion-cells, of motor nerve-fibres with

M = motor effect: *i.e.* increase of tone; augmentation or acceleration of rhythm.
I = inhibition: *i.e.* relaxation of tone; cessation, weakening or slowing of rhythm.

	Effects of stimulating sympathetic nerve-supply, or injecting adrenaline intravenously	
Organ	Before ergot	After ergot
Arteries (cat, dog, ferret)	M	I
,, (rabbit)	M	Nil or weak M
Cardiac muscle	M	Nil or weak M
Spleen (cat)	M	I
Stomach (cat)	I	I
Small intestine (cat, dog, monkey)	I	I
Large intestine (cat)	I	I
Ileo-colic sphincter (cat)	M	Nil
Internal anal sphincter (cat)	M	I
Gall-bladder	I	I
Fundus of urinary bladder (cat)	I	I
Fundus of urinary bladder (ferret)	M	I
Base of bladder and urethra (cat)	M	Nil
Pilo-motor muscles	M	Nil
Dilatator iridis	M	Nil with adrenaline Weak M with cervical sympathetic
Uterus (cat, non-pregnant)	I or M & I	I
Uterus (cat, pregnant)	M	I
Uterus (rabbit)	M	I (slight)
Uterus (monkey)	M	I
Retractor penis (dog)	M	Nil

skeletal muscle, of postganglionic fibres, belonging to the cranial and sacral division of the autonomic systems, with involuntary muscle—all these therefore escape paralysis. The undiminished effect of pituitary extract shows that involuntary muscle, from whatever system innervated, retains its contractile function. The paralytic effect can, therefore, be definitely limited, in the first-place, to the structures which adrenaline stimulates—the so-called myoneural junctions connected with the true sympathetic or thoracic-lumbar division of the autonomic nervous system. But the limitation of the effect is narrower than this. The accompanying scheme tabulates the changes produced by excessive doses of ergot in the reaction of the different organs examined to adrenaline or to stimulation of their sympathetic nerve-supplies.

The organs in the above table fall naturally into three groups corresponding to the types of reaction.

(1) Those with an inhibitory nerve-supply from the sympathetic system:—the stomach and intestines, the gall-bladder, the fundus of the urinary bladder in the cat, and the non-pregnant uterus in the same animal. In these, ergot produces no change, in the effect of stimulating the sympathetic nerves or in the parallel effect of adrenaline; except when, as sometimes in the cat's non-pregnant uterus, a preliminary motor phase of reaction occurs. The latter is then abolished, leaving pure inhibition as the subsequent response.

(2) Those in which a normal purely motor sympathetic effect is reduced by ergot to a minimum, or below the limits of perception. Such are the rabbit's arteries, the heart, the ileo-colic sphincter, the base of the bladder of the urethra, the dilatator iridis, the pilo-motor muscles, and the retractor penis (dog). It is noteworthy that this group contains all those structures in which the motor effect showed especial resistance to paralysis.

(3) Those in which the normal effect is motor, the effect after ergot inhibitory. In this group are the arteries of carnivora; the cat's spleen and internal anal sphincter; the fundus of the ferret's urinary bladder; and the uterus of the rabbit, monkey, and in some cases of the cat.

Several possibilities suggest themselves in explanation of the above changes. Brodie and Dixon[1], finding that the blood vessels of the lung dilated slightly when adrenaline was added to a perfusion fluid, attributed the phenomenon to direct action on muscle-fibres not

[1] This *Journal*, xxx. p. 488. 1904.

innervated from the sympathetic system. It might be suggested that ergot reduced all plain muscle-fibres to this condition, by paralysing the structures, associated with sympathetic innervation, on which adrenaline normally acts. Such a view, however, fails altogether to account for the facts (1) that not all motor effects of adrenaline are replaced by inhibition, some being simply abolished: (2) that stimulation of sympathetic nerves and injection of nicotine produce the same abnormal inhibitor effects as does adrenaline: (3) that the normal inhibitor actions of adrenaline and sympathetic excitation not only escape abolition by ergot, but preserve their normal type unchanged.

Another explanation, which might be suggested, is that plain muscle, throughout the body, is thrown by ergot into such a condition of tone that it responds by relaxation to stimuli which normally cause it to contract. This view, however, is not in accordance with the facts. The tone of the cat's internal anal sphincter is lowered by toxic doses of ergot: yet it relaxes under these conditions in response to stimuli which cause it to contract under normal conditions, when its initial tone is higher. Similarly, with large doses of the drug, the tone of the arteries is eventually brought below the initial level: none the less adrenaline then produces a still further vaso-dilator fall of blood-pressure. That some motor sympathetic effects are reversed, others simply reduced or abolished, and that the motor effects of autonomic nerves of cranial and sacral root origin are retained in full vigour, are facts for which this hypothesis provides no explanation—facts with which, indeed, it is inconsistent.

The only explanation which fits all the facts is that the paralysis, already shown to be confined to the myoneural junctions of the true sympathetic system, is further limited to those of motor function, leaving those concerned with inhibition relatively, or absolutely unaffected. The three types of reaction indicated by the above classification are then accounted for by saying that, in the first group, the myoneural junctions, being predominantly inhibitor, are not perceptibly affected: in the second group, being purely motor, they are simply paralysed: in the third group, being mixed, but predominantly motor, they undergo a reversal of function, since paralysis of the normally preponderant motor elements allows the emergence of a normally masked inhibitor effect.

Great support is afforded to this view by the behaviour of the cat's uterus, in which the normal reaction to adrenaline or sympathetic stimulation varies with the functional condition. In such a case there

is clear ground for assuming the existence of a mixture of motor and inhibitor elements in the sympathetic nerve-supply, of which one or the other becomes functionally predominant according as the animal is or is not pregnant. It has been shown that the reaction of the cat's uterus, after ergot paralysis, to adrenaline or stimulation of the hypogastric nerves, is uniformly inhibition. We can only suppose that, in the non-pregnant animal, the predominant inhibitor elements retain, after ergot, their normal activity, and that, in the pregnant animal, the predominant motor elements are deprived by ergot of their function, the inhibitor admixture being thereby revealed.

Similarly, as has been indicated already, the analogy of the effect in the rabbit suggests that the sympathetic innervation of the cat's internal anal sphincter is really of mixed function. In the sympathetic nerve-supply to the ferret's bladder, again, the analogy of the cat suggests the presence of masked inhibitory elements. In both cases the obvious effect of stimulation under normal conditions is motor: ergot paralysis brings to light the inhibitor admixture.

If this explanation be thus applied to cases where the presence of masked inhibitory elements was known or suspected on other grounds, it must be extended to the other cases in which stimulation of the sympathetic nerves or injection of adrenaline causes, after ergot, an inhibitor in place of the normal motor effect, viz. the spleen (cat) and the arteries of all the carnivora examined. In the case of the arteries the presence of inhibitor elements in the sympathetic supply is, again, not a new suggestion. Dastre and Morat[1] obtained vaso-dilator effects in the bucco-facial area by stimulation of the dog's cervical sympathetic: Bradford[2] found evidence for the existence of vaso-dilator fibres in the nerves to the kidney, Bunch[3] in those to the dog's intestine; and Bayliss[4] concluded that some part of the fall of pressure produced by exciting the depressor nerves was due to reflex excitation of vaso-dilator fibres to the splanchnic area. Later Bayliss[5] was inclined to attribute all these effects to antidromic impulses in dorsal-

[1] Dastre and Morat. *C. R. Acad. des Sciences*, XCI. p. 393. 1880. Also Langley and Dickinson. *Proc. Roy. Soc.* XLVII. p. 380. 1890. I have myself recently observed this bucco-facial dilation in a dog, and it persisted after a dose of "cornutine" which abolished the pressor effect of adrenaline and the secreto-motor effect of the cervical sympathetic. The pupil, however, still dilated somewhat.

[2] Bradford. This *Journal*, x. p. 358. 1889.

[3] Bunch. This *Journal*, XXIV. p. 86. 1899.

[4] Bayliss. This *Journal*, XIV. p. 303. 1893.

[5] Bayliss. This *Journal*, XXVII. p. 280. 1902.

root fibres: but it is very improbable that the vaso-dilator effects obtained after ergot paralysis are of this nature. The effect is produced by adrenaline even better than by excitation of the nerves, and the facts known as to the action of that substance give no warrant for attributing any of its peripheral effects to excitation of structures other than those associated with innervation by fibres of the true sympathetic system. (Cf. Elliott, *loc. cit.*)

It is evident that, in these cases of sympathetic innervation of mixed function, the motor elements need not be completely paralysed in order that the normal motor effect may be reversed. Short of complete obliteration the motor stimulus may be so weakened as to be overcome by the more resistant inhibitor: just as, under normal conditions, the inhibitor is completely masked by the preponderant motor effect. The balance is normally on the motor side: ergot paralysis turns the scale in favour of inhibition.

That being so we shall expect to find, in cases where the sympathetic nerve-supply is purely motor, a greater resistance of the motor response to the action of ergot. This was actually found in several cases. The pilo-motor and cardio-accelerator effects required large doses for their abolition. The base of the bladder in some cases still showed a feeble contraction when observed directly, and the pupil in all cases still dilated slightly after the largest doses of the drug. These are cases in which the detection of a small remnant of reaction is especially easy. In the case of the iris there is the further possibility that the slight persistent effect is due, not to contraction of the dilator, but to inhibition of the sphincter. But there is no good ground for supposing that the paralysis of the sympathetic motor myoneural junctions is, in any case, absolutely complete to all strength of stimulus. The most that can be said is that in most cases the motor effects are reduced below the threshold of perception.

The experiments give no indication as to the level at which functional differentiation occurs. A sympathetic nerve-supply of mixed function may contain some fibres connected to purely inhibitor, others to purely motor myoneural junctions: or, on the other hand, the myoneural junctions may themselves be composite, containing both motor and inhibitor elements. The question as to whether these so-called myoneural junctions are morphologically differentiated, or, as Langley suggests, distributed, as "receptor substances" through the muscle-fibre is also untouched by these results. One thing is clear: the structure or substance affected by adrenaline is also that which reacts to impulses

in sympathetic nerve-fibres, for the two kinds of motor stimulus suffer a similar extinction by ergot. The effects may therefore be summarised by saying, that ergot contains a principle which has a paralytic action on the motor elements of that myotrophic structure or substance which is excited by adrenaline and by impulses in fibres of the true sympathetic system; the inhibitor elements of the same being relatively or absolutely unaffected.

One of these peripheral paralytic effects has been purposely excluded from the above summary and discussion. To class the secretory effect of sympathetic nerves and of adrenaline as motor and to quote its abolition by ergot in support of the above generalisation is not justifiable. There is no good reason *à priori* for classifying the secretory effect with either the motor or inhibitor effects on plain muscle. On the other hand, there seems good ground for a deduction in the reverse direction; the fact that the sympathetic secretory effect is abolished by ergot shows that the gland-cell structures[1] affected by adrenaline and sympathetic impulses are, to that extent, biochemically equivalent to the motor rather than the inhibitor myoneural junctions[2].

The reaction has already had practical application in furnishing a means of direct demonstration of the presence of inhibitor elements in a predominantly motor sympathetic nerve-supply. Good evidence was already available for the view that the inhibitor effects of sympathetic nerves and adrenaline are independent of the anæmia which in most cases accompanies them. The discriminating paralysis here described adds another and, apparently, a conclusive proof of that supposition. In both these directions the reaction will probably find use in future physiological experiments.

Note on the general effects of the preparations used.

Apart from the phenomena already described in detail the most marked effects of active ergot preparations are on the central nervous system[3]. Convulsant effects were described by Kobert as characteristic

[1] To make the nomenclature consistent some such term as "cyto-neural junction" would be needed.

[2] This is, apparently, not true of those structures in sweat-gland cells which respond to excitation of sympathetic fibres. In a recent experiment I found the sweat secreted abundantly on the hind foot of the cat when the abdominal sympathetic was stimulated after 5 mgms. of cornutine.

[3] We are dealing here with preparations free from ergotinic acid, and the spinal paralysis produced by that substance is, therefore, not in question.

of cornutine: but it is noteworthy that with intravenous injections he produced convulsions also with his "sphacelinic acid." Respiratory paralysis was observed by Kobert with "cornutine" and "sphacelinic acid," and by Jacobj with "sphacelotoxin."

I have made no complete and deliberate experiments on this aspect of the action, but certain points noted incidentally are worth mentioning. The confirmation of the paralytic effect on the respiratory centre has been noted. The vaso-motor centre seems also to be paralysed. After excess of the ergot-preparations stimulation of the depressor or other sensory nerve causes neither rise nor fall of blood-pressure: whereas if, as Bayliss argues, the depressor acts partly by reflex stimulation of vaso-dilators, this part of its action should persist, and one would further expect a depressor action from other sensory nerves, as after chloral, unless the vaso-motor centre were itself thrown out of action.

Convulsions are produced by all the preparations used. It has already been hinted that the "stimulant" and "paralytic" effects dealt with in the preceding sections may be due to different principles. This is rendered probable by the varying prominence of the two sets of effects with different specimens of the various preparations. In the cases where I have made the observation the central, convulsant effect has been more powerful in those preparations giving the peripheral, sympathetic paralysis in small dosage. The evidence on these points is yet far from complete: but it seems worth while to indicate that a mixture of two principles—a "stimulant" and a "paralytic and convulsant" principle—in different proportions would sufficiently account for all the physiological differences described by Kobert as distinguishing "cornutine" from "sphacelotoxin" (sphacelinic acid). For example, the presence of a comparatively small amount of the "paralytic" principle in sphacelinic acid might protect the sensitive cat from the action of the "stimulant" substance, but allow the latter to produce gangrene in the far more resistant fowl. On the other hand, a high proportion of paralytic principle in cornutine would protect even the fowl from gangrene and, at the same time, give to cornutine the marked convulsant activity attributed to it.

General Conclusions.

The main conclusions arrived at may be summarised as follows:—

(1) The physiological effects of preparations from ergot, such as cornutine and sphacelotoxin, fall naturally into two groups:

(*a*) Stimulant effects on plain-muscular organs, prominent among which are contraction of the arteries, the uterus, and the sphincter of the iris.

(*b*) A specific paralysis of the motor elements in the structures, associated with sympathetic innervation, which adrenaline stimulates: the inhibitor elements retaining their normal function, as do also both motor and inhibitor autonomic nerve-supplies of cranial and sacral root-origin.

(2) It is probable that these two sets of effects are produced by different active principles, of which the one responsible for the peripheral paralysis appears also to be concerned in the central convulsant effects described by Kobert and others.

Incidental conclusions, which appear to have an interest of their own are:—

(1) That in the sympathetic nerve-supplies to the arteries and spleen of carnivora, the internal anal sphincter of the cat, and the bladder of the ferret there exists an inhibitor constituent normally obscured by the preponderant motor-effect.

(2) That the sympathetic nerve-supply to the uterus of the non-pregnant cat is almost purely inhibitor in effect: when the cat becomes pregnant the effect becomes motor, and the inhibitor constituent can then be revealed by the discriminating paralysis caused by ergot.

(3) The pressor principle of the pituitary (infundibular portion) acts on some constituent of the plain muscle fibre other than that which is excited by adrenaline and by impulses reaching sympathetic axon-endings.

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