# THE PHYSIOLOGICAL EFFECTS OF EXTRACTS OF THE SUPRARENAL CAPSULES. By GEORGE OLIVER, M.D., AND E. A. SCHÄFER, F.R.S.

*(From the Physiological Laboratory, University College.)*

## I. RESULTS OBTAINED BY PREVIOUS OBSERVERS*.

Pellacani, both alone[1] and in conjunction with Foà[2], appears to have been the first to investigate the effect of injecting extract of suprarenal capsule into animals. These observers used for the most part filtered aqueous extract of fresh suprarenal of the dog and calf, administering it subcutaneously. The following are some of the results which they obtained:—In a dog weighing 2,700 grammes having injected nearly the whole of an extract of neutral reaction made from two suprarenals of the calf, they observed on the same day no effect; temperature, respiration and the heart's action remaining normal: on the following morning, however, they found the animal dead. In a guinea-pig weighing 770 grammes they injected five grammes of an aqueous extract; this amount containing the active principles extracted by water from about one-quarter of a gland of the calf. They note that twelve hours after injection the animal refused food, and that the temperature was lowered by one degree. One hour later the animal was found dead. Similar results were obtained in rabbits. They further injected into rabbits extracts from the liver of the calf and from the kidney of the calf, the injection being made into the jugular vein. In these cases also they found that death was produced. They seem to infer that the effect is a general one, common to many gland extracts. In a further research an extract equivalent to one gramme of the capsules, neutralised by soda, was injected under the skin of a dog weighing five kilogrammes. The animal soon became agitated, and was attacked by vomiting; the respiration became irregular and was dyspnœic. This was followed by somnolence and general prostration, the temperature remaining normal. This condition lasted six hours. The next morning the animal was found completely paralysed, sensibility was lost, the respirations were frequent and superficial. Death ensued nineteen hours after the injection and was produced apparently by suspension of respiration. In another dog, weighing nearly thirty kilogrammes, fifteen cubic centimetres of a strong watery extract made by digesting six capsules from the ox in 50 c.c. of water were injected into a vein. This produced dyspnœa, agitation, frequency of cardiac beats, and subsequently diminished frequency. The respirations became more superficial and the heart-beat diminished in force. There was an evacuation of the bowel. Four

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* An epitome of recent observations, anatomical, physiological and pathological, on the suprarenal capsules is given by H. D. Rolleston in the *British Medical Journal* of March and April of this year (Gulstonian Lectures).

hours afterwards the temperature had gone up from 39° C. to 41·2; an hour later it was 40°; four hours later 38°, accompanied by great prostration.  In another half-hour the animal died.

In the frog these observers found that injection of the extract into the dorsal lymph sac was followed in about fifteen minutes by slowness of movement, the reflexes however being persistent.  After twenty minutes the animal had ceased to move when placed on its back, and its sensibility and reflexes appeared diminished.  Twenty-five minutes after the injection paralysis was general.  Nothing is said about recovery.

In most other animals, *e.g.* rabbits, Foà and Pellacani found that although after subcutaneous injection the animal appeared for the time to be unaffected, it was invariably found dead the next morning.  The statements of these investigators have been called in question by Alexander[3] and Mattei[4].

Marino-Zucco[5] has also published the results of some experiments as to the effect of extracts of suprarenal capsules.  He obtained from these organs considerable amounts of neurin and seems early to have come to the conclusion that the physiological results got from the extract were due to the action of this substance; and in this conclusion he appears to have been confirmed by observations made in combination with Dutto[6], which showed that in disease of the suprarenal capsules neurin makes its appearance in the urine.  A further series of communications by Marino-Zucco in combination with Guaruceri[7] lead to the same result, viz. that the toxic action of watery extracts of suprarenal capsules is due to their containing neurin.

With the exception of two communications by Alexais and Arnaud[8], which we have been unable to consult, these are the only published observations that we have been able to discover with regard to this subject.  None of the above observers mentioned seem to have investigated the effects of the extracts upon the blood-pressure, nor to have given graphic records illustrating their statements, which rest almost entirely upon direct observation of the animals employed.

In connection with this subject, although not strictly speaking a part of it, we may briefly allude to the observations which have been made regarding the toxicity of extracts of the muscles in animals which have been deprived of their suprarenal capsules.  We do not propose to refer at any length to the effects of this operation, preferring to reserve this subject for another communication.  But it may be briefly said that our own results agree with those of Tizzoni[9] and of most recent observers which have served to confirm the conclusions of

Brown-Séquard[10], viz. that extirpation of the suprarenal capsules is invariably followed sooner or later by death, and that the symptoms during life are those of extreme muscular prostration. Now it has been stated by Abelous and Langlois[11] that in animals which have been deprived of their suprarenal capsules the blood and the muscles contain a toxic substance which produces similar prostration in other animals, and especially in those which have been recently deprived of their capsules, but which have not yet shown any toxic symptoms; and they infer from the results of this experiment that the suprarenal capsules have the function of getting rid of a toxic substance which is produced in the muscles and which accumulates in the blood; and that deprivation of the capsules causes this substance to accumulate in both blood and muscles. The general effects of the toxin are compared by them to those of curare; and the results which were obtained by Foà and Pellacani (especially the muscular paralysis which is caused, according to them, by the injection of suprarenal extract) have also been compared with the effect produced by curare. We refer to these observations because, as will presently appear, the results which we have ourselves obtained from the action of suprarenal extract upon the muscular system are in no way comparable to those produced by curare.

We have made two preliminary communications of our results, accompanied by demonstrations, to the Physiological Society, in March, 1894, and in March, 1895, respectively *.

## II. The Suprarenal Extracts employed in this research. Their mode of preparation and administration.

The suprarenals employed by us have been obtained mainly from the calf, but also from the sheep, the guinea-pig, the cat, the dog, and from man. The physiological effects which we have noticed have been identical in all, the only difference being in the case of diseased suprarenals in man (Addison's disease); in which case, if the disease be extensive, no effect whatever is obtained.

Extracts of the glands were prepared with water, with alcohol of various strengths, and with glycerine. They were made either by digesting an ascertained weight of the fresh gland or of the dried gland in these menstrua, or, in addition, by boiling the infusion for a few minutes. The effects were equally pronounced whether in the form of infusion or in that of decoction, and whether the extract were made with pure

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* See this *Journal*, xvi. p. i. and xvii. p. ix.

water, with diluted alcohol or with glycerine. When an extract made
with alcohol or with glycerine was injected it was diluted with water or
salt solution and an equivalent amount of alcohol and glycerine diluted
with water to the same extent was injected into the animal as a control.
Extracts were also prepared with absolute alcohol, ether, nigroïn, and
various other solvents. Such extracts were evaporated to dryness and
the residue was either dissolved or suspended in water or salt solution
and thus injected. With alcohol and ether absolutely free from water
no active principle whatever was extracted by those fluids provided that
perfectly dehydrated gland substance was used for the abstraction. The
presence of a small amount of water in the alcohol or the water which
enters into the composition of the normal fresh gland was sufficient to
enable the alcohol to take up a certain amount of active material. Care
has always been taken to employ solutions which had been filtered free
from all obvious particles. In most of our earlier experiments an aqueous
decoction representing one part of suprarenal capsule to six of water or
normal saline was used for injection. In our later experiments the
dried glands were for the most part employed for the preparation of the
extract, and the solution used was 1 part of the dry material to 18 of
water or normal saline. In some cases we have used a decoction con-
taining 1 part of the dried gland to 100 of water, or even a weaker
extract than this.

The animals which we have experimented upon have been chiefly
dogs, but we have also made a certain number of experiments upon cats,
rabbits, and guinea-pigs, and one upon a monkey. For all experiments
involving vivisection, chloroform or ether, but usually chloroform, has
been the primary anæsthetic, this being followed by subcutaneous
injection of morphia, and in some cases of atropine. We have sometimes
employed curare, but it can only be used in very moderate doses since it
tends to antagonize the effect of suprarenal extract upon the blood
vessels and to some degree upon the heart.

The extracts have been usually administered by intravenous injec-
tion, in which case a fine metallic cannula has been tied into a peripheral
vein, and the extract injected directly from the hypodermic syringe into
this. In all cases we have taken the precaution of washing out what
little extract may have remained in the cannula, and in the portion of
the vein to which it was tied, with normal saline solution. In some
instances we have administered the water-extract by the mouth and in
others by subcutaneous injection, thus repeating the experiments of Foà
and Pellacani; it will be shown later with what results. We have

further injected the extracts, diluted largely with normal saline solution, through the arterial system of the frog, the brain and spinal cord of which had previously been destroyed, in order to determine whether it produces a direct effect upon the blood vessels.

Although we have occasionally employed larger doses for intravenous injection, in by far the majority of our experiments we have not injected more of the extract than was equivalent to 0·2 gramme of the fresh gland. Even this minute dose is much more than enough to produce the maximum effects upon the heart and blood-pressure, and in our later experiments we have adopted as a sufficient dose for intravenous injection 1 minim of a 1 in 18 decoction of the dried gland. This is equivalent to 0·0037 gramme of the dried gland or to 0·015 gramme of the fresh gland (taking the proportions of water in this at about 80 %). This dose still gives the maximum effect upon the heart and arteries of a dog weighing 10 kilogrammes. One and a half milligrammes therefore of the fresh gland per kilogramme of body weight is sufficient to produce the maximum effect upon the vascular system. But, as will presently appear, the active principle of the extract is contained in the medulla alone, and one and a half milligrammes of the whole gland could not be reckoned to contain more than half a milligramme of medulla. Of this some four-fifths would be water, and by far the greater part of the remaining fifth, proteid substances, which do not pass into solution in the decoction. The actual amount of the active principle therefore in a dose which produces a maximum effect upon the circulatory system is infinitesimally small, and it is only by using extremely small quantities of a highly diluted extract that a submaximal effect has been obtained. This we have done when we desired to compare the relative strengths of extracts prepared in the same manner from the suprarenal capsules of different animals. Our experiments in this direction have however up to the present led to no very definite conclusion.

### III. THE PHYSIOLOGICAL EFFECTS OBSERVED.

#### (a) *General effects.*

We have injected subcutaneously comparatively large doses of aqueous suprarenal extracts into the dog, the guinea-pig, and cat without obtaining any obvious effect. The animals were usually unaffected by moderate doses, but with larger doses in the guinea-pig and the dog we have observed a slight transitory disturbance of the rate of the heart-beats, of the respiration, and of the body temperature.

For example, in a small dog weighing 1·75 kilogrammes, after the subcutaneous injection of an aqueous extract equivalent to 15 grammes of the fresh gland the following alterations of the pulse-rate, of the respiration and of the rectal temperature were observed.

|  |  |  |
|---|---|---|
| Before injection |  | Pulse-rate 116 |
| ,, | ,, | Respiration 28 |
| ,, | ,, | Temperature 38·8° C. |
| 30 mins. after injection |  | Pulse-rate 140 |
| ,, | ,, | Respiration 30 |
| ,, | ,, | Temperature 39·2° |
| 60 ,, | ,, | Pulse-rate 130 |
| ,, | ,, | Respiration 22 |
| ,, | ,, | Temperature 39·05° |
| 90 ,, | ,, | Pulse-rate 150 |
| ,, | ,, | Respiration 20 |
| ,, | ,, | Temperature 38·8°. |

But notwithstanding these disturbances the animal appeared quite well, and on the following morning was as lively as usual. A guinea-pig weighing 0·514 kilogramme and having a rectal temperature of 37·5 C. was subcutaneously injected with an aqueous extract equal to 1·29 gramme of the fresh gland at 11.30 A.M., when the following variations of temperature were observed.

|  |  |  |
|---|---|---|
| At | 12 A.M. | 36·54° |
| ,, | 12.30 P.M. | 36·66° |
| ,, | 1.0 ,, | 34·75° |
| ,, | 1.30 ,, | 35·90° |
| ,, | 3.0 ,, | 36·30°. |

The only apparent general effects were a listless quiescent condition and refusal of food on the day on which the injection was made; but on the following morning the animal was as well as usual.

In the rabbit the case was different. In this animal a large dose of suprarenal extract administered subcutaneously appears invariably to produce death; and this event may take place in half-an-hour, or it may be delayed until the following day, or it may not occur until after the lapse of a few days. After the injection the temperature (taken in the rectum) may fall and may become very low before death, or it may be but slightly affected on the day of injection, and yet the animal may be found dead the following morning. In half-an-hour after a large subcutaneous dose the animal may become listless, and may when interfered

with move languidly; it may however preserve its normal movements in the hours following the injection and yet may die during the night.

The following are typical examples of observations supporting these conclusions.

1. A rabbit full grown, breathing at the rate of 85 per minute, and having a rectal temperature of 39·15° C. at 11.45, was injected under the skin of the back with suprarenal extract equivalent to 1·29 gramme of the gland. 12.15, R. 64—8 and T. 37·75° C., movements slightly languid. Extract equal to 0·97 gramme of the gland injected. 12.45, R. 64 and T. 36·9°. A further injection equal to 0·97 gramme of the gland was made. 1.15, R. 61 and T. 36·0°. Extract equal to 0·97 gramme of the gland was injected. 1.45, R. 64, T. 36·65°. 2.15, R. 76, T. 36·9°. An equivalent of 1·94 gramme of the gland injected. 2.45, R. 64, T. 36·1°. Extract equal to 0·645 gramme of gland injected. 3.15, R. 68, T. 37°. No further injection made. 5.15, R. 68, T. 37·1°. At 11 on the following morning the animal was found sitting in a corner and when disturbed its movements were observed to be slow and languid. It refused food. R. 40—50, T. 35·4°. At 3 p.m., R. 39, T. 35°. For 7 days before death, which occurred on the 9th day, the animal remained in a languid state, taking little or no food, with a low temperature (varying from 35° to 36°) and slow superficial and irregular respiration. The limbs twitched every now and then on attempting to rise and eventually the hindlegs became paralysed. The conjunctival reflex was retained and the pupils were not dilated.

2. Two rabbits were taken of nearly equal weight (1·8 kilogramme). One was subjected to subcutaneous injection of suprarenal extract, and the other (as a control) to subcutaneous injection of salt solution. The rectal temperature of the former was 39·10° and of the latter 38·35°. An extract equal to 2·58 grammes of the gland was injected under the skin of the back at 11.45. At 12.15 the suprarenal rabbit was seized with clonic convulsions which quickly passed off. The rectal temperatures at 12.45, 1.45, 2.45, and 3.45 were 38·10, 35·85, 34·85, and 35·4; while those of the control rabbit remained without any appreciable alteration and only once fell to 38·15. The respiration remained after the injection shallow and hurried all the day— being 150 as compared with 100 in the control rabbit; and the movements by the animal were languid. On the following morning the suprarenal rabbit was found dead in its hutch.

3. A rabbit, weighing 1·9 kilogramme, and having a rectal temperature of 37·15 and respiration 48 was injected under the skin of the back with extract equal to 2·58 grammes of the gland. In 30 minutes the temperature was found to be higher and the respirations more frequent and irregular (T. 37·75°, and R. 60—80); and the heart's action had become very rapid.

The movements of the animal however remained normal. A further injection of extract equivalent to 0·65 gramme of the gland was made. In 30 minutes more the temperature was found to be 36·90° and the respiration 60 ; and the movements remained normal. Notwithstanding this apparently favourable condition the animal was found dead on the following morning.

4. A rabbit weighing 2·55 kilos, and having a rectal temperature of 37·6°, was injected under the skin of the back with an extract equivalent to 6·45 grammes of the gland. A control rabbit was injected with salt solution. In 5 minutes we observed in the suprarenal rabbit violent and frequent action of the heart and rapid shallow breathing. In 10 minutes the animal showed sudden symptoms of distress, fell over upon its side, and had a rectal temperature of 37·1 ; and in 35 minutes after the injection was made, death took place suddenly and without convulsions. Post-mortem examination failed altogether to reveal the cause of death. In another rabbit of less weight (1·40 kilogramme) the subcutaneous injection of extract equal to 3·225 grammes of the gland produced death in 30 minutes. In this case in 10 minutes after the injection the movements of the animal became much less active and the heart's action increased considerably in force. Death took place quite suddenly and an immediate post-mortem examination did not reveal the cause of it. The heart chambers were all contracted, and no clots were found. Furthermore, in all the cases in which the animals were found dead the morning following the injection or after a longer interval the cause of death has not been revealed by post-mortem inspection.

From the observations we record later on as to the effect of the gland-extract upon the respiration we should not anticipate that death had been produced by paralysis of the respiratory centre. It is however possible that the material obtained from the gland, which—in rabbits only in our hands—has produced death under these circumstances, is of different nature from that which has such an extraordinary activity in stimulating the muscular tissue of the heart and blood vessels when injected into a vein.

With smaller subcutaneous doses than were employed in the foregoing experiments, but doses which injected into the veins would produce an enormously powerful physiological effect, we have failed to detect any indications of disturbance of function, either on the day on which the injections were made, or on the following day.

The general effects of the subcutaneous injection of suprarenal extract in the frog in a dose equivalent to 0·3 gramme of the fresh gland are sufficiently striking. For the first few minutes the animal appears to be unaffected. After about 10 minutes its movements have usually become languid, but if held by the leg it is still able to kick with great

force. After another 5 minutes its voluntary power over the muscles is greatly diminished and it reacts little if at all to cutaneous excitation. It is quite unable to recover itself if laid on its back. Soon however this condition begins to pass off so that by half-an-hour after the dose has been administered the animal again appears to be nearly, if not quite, in a normal condition. Even considerably larger doses are re-covered from within a comparatively short time. That the paralysis is not peripheral like that produced by curare is shown by the results of stimulating the muscle-nerve preparation when the effect is at its height (see p. 264 and fig. 20): it must therefore be due to the action of the poison upon the central nervous system. The languid movements which are manifested may be the result of the effect which the extract has in prolonging the individual contractions of the muscle fibres.

### (b)  Effects on the arterial system.

The methods which we have employed for determining the effects of suprarenal extract upon the arterial system are

1.  The ordinary mercurial kymograph.

2.  Plethysmographs of various kinds and adapted to various organs, such as the ordinary plethysmograph of Mosso for the limbs and the oncometers of Roy for the spleen and kidney.

3.  The perfusing of Ringer's circulating fluid containing supra-renal extract through the arterial system of the frog after the nervous system had been destroyed; noting the result of the passage of the extract in altering the rate of flow through the blood vessels.

4.  The results of direct ocular evidence upon both the large and the small blood vessels.

All the above modes of observation have given marked evidence of contraction of the arterioles (figs. 1, 2 and many others). This con-traction is so great as to produce (even when concomitant vagus action has caused a great diminution in the rate and force of the heart's beats) a large rise of blood-pressure, and, in the case of the frog, with its nervous system destroyed, almost complete cessation of the flow of circulating fluid through the arterioles. This contraction of the arterioles, thus producing as it does a great rise of blood-pressure within the arterial system, causes a passive expansion of the larger and medium sized arteries, so that these vessels are seen to swell almost to bursting, and to be proportionately elongated. The effect of the con-traction of the arterioles upon an isolated organ enclosed by a plethys-mograph is different according as this passive swelling is well marked

or not. The usual effect of the extract is to produce contraction of such isolated organs. The limb shrinks in size (figs. 8, 9), the kidney diminishes greatly in volume (fig. 2), and the spleen contracts enormously (figs. 3, 4), while the heart and the larger blood vessels are enormously distended. Sometimes however an organ, especially a limb, expands (figs. 2, 7).
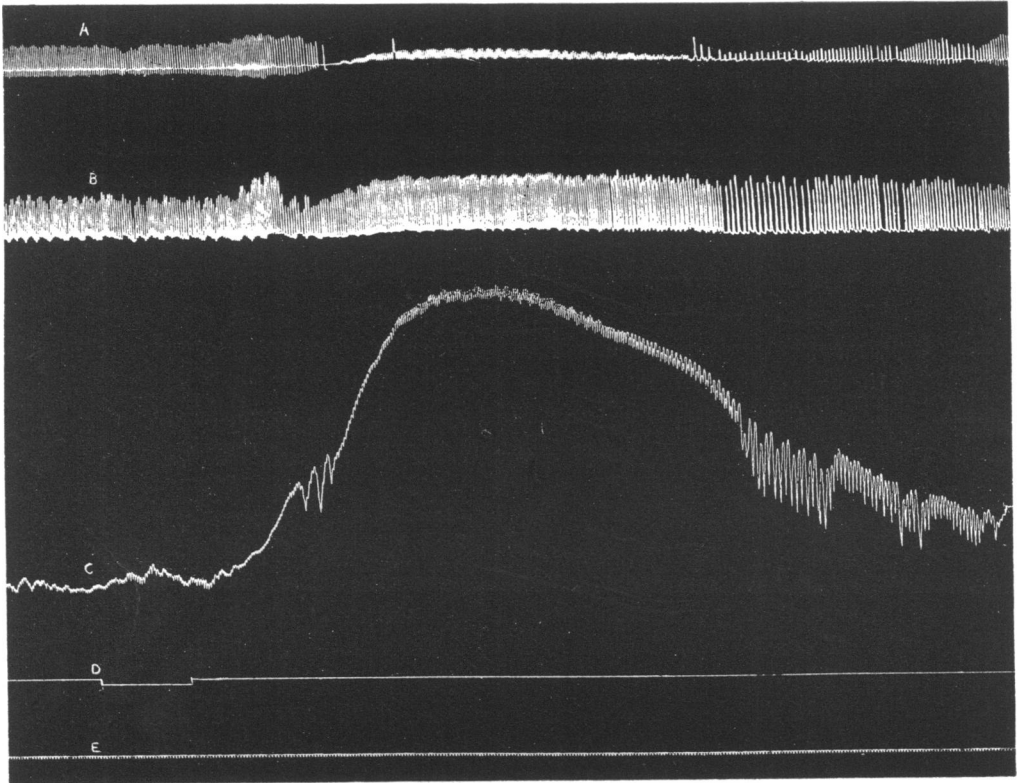


Fig. 1. Dog, weight 16 kilos. Chloroform, afterwards morphia. Vagi uncut. Effect of injecting extract of 0·2 gramme dog-suprarenal. Delayed inhibition.
*A*, auricle; *B*, ventricle; *C*, femoral artery; *D*, injection of suprarenal (watery extract), the line *D* also indicates 0 pressure; *E*, time in 0·5 sec.*

In some experiments where two or more organs (such as the right and left fore-limb, or one fore-limb and one kidney) were under investigation at the same moment one was found to contract and another to expand (figs. 2, 4, 6, 7), the former owing its contraction to the active dimi-

* All the curves except those given in fig. 12 are to be read from left to right. They are photographically reproduced and are for the most part half the actual size.
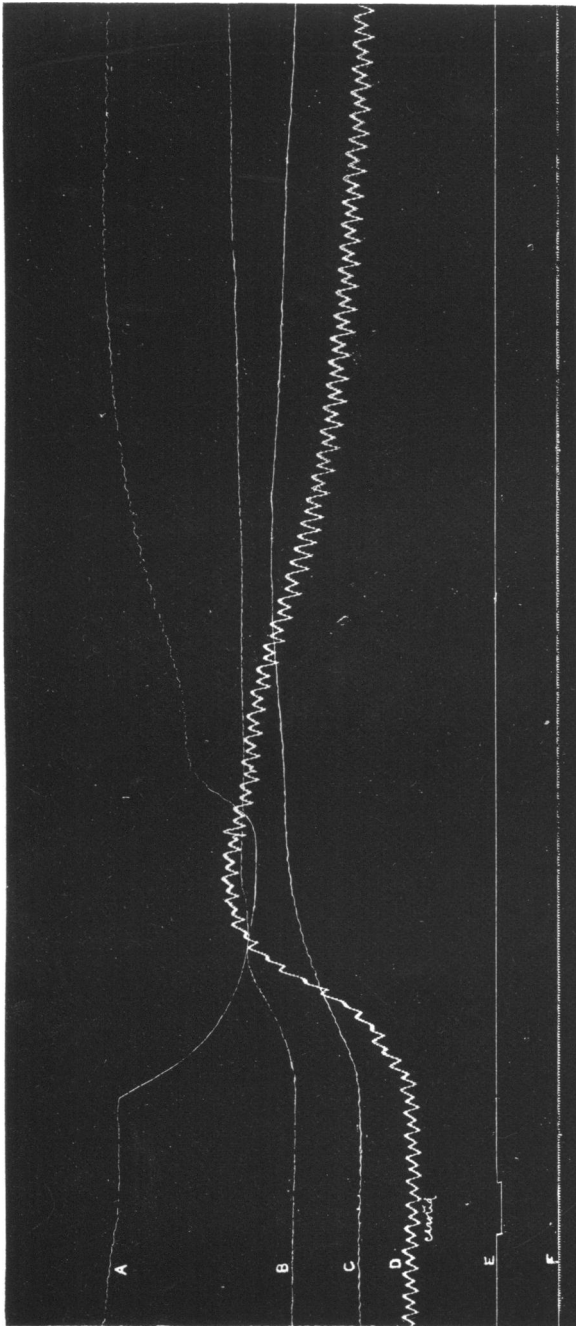
Fig. 2. Dog, 24 kilos. Morphia, curare (small dose). Vagi cut. Brachial plexus cut on right side, uncut on left. A, kidney volume (oncometer); B, volume of right arm; C, volume of left arm; D, carotid; E, blood-pressure abscissa; F, time 0·5″.

Effects of intravenous injection of 0·1 gramme calf-suprarenal (spirit extract).
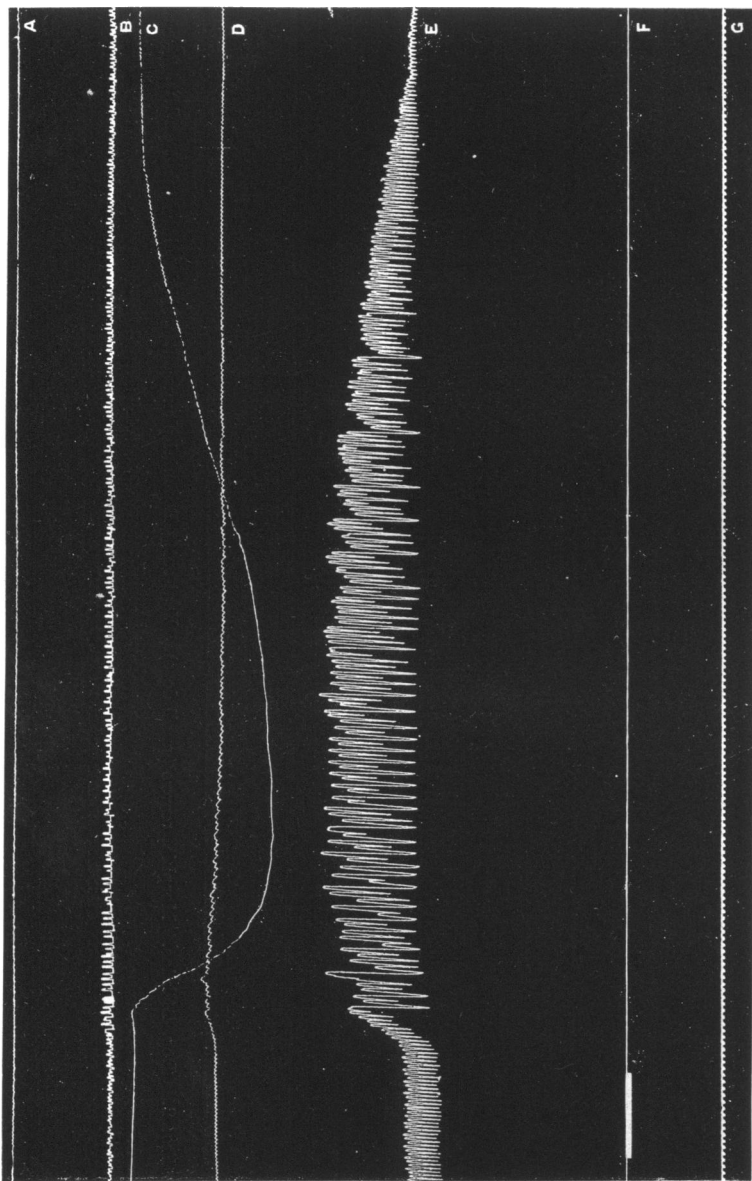
FIG. 3. Dog, 9·25 kilos. Morphia only.

*A*, auricle (very slight indications); *B*, ventricle; *C*, spleen volume (oncometer); *D*, arm-volume; *E*, femoral; *F*, abscissa and signal; *G*, time 1″.

Effects of intravenous injection of ·0037 gramme calf-suprarenal (decoction).
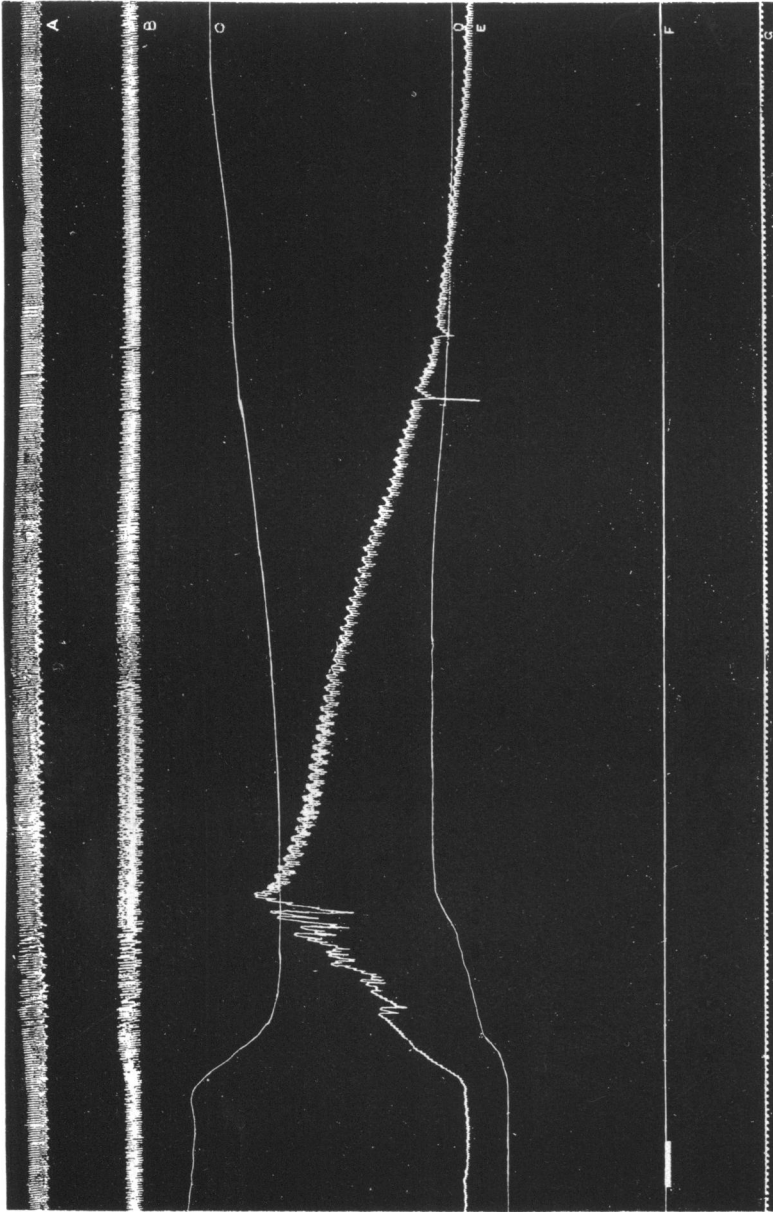
Fig. 4. Dog, 9·25 kilos. Morphia, atropine.

*A*, auricle; *B*, ventricle; *C*, spleen; *D*, arm-volume; *E*, blood-pressure (femoral); *F*, abscissa and signal; *G*, time 1″.

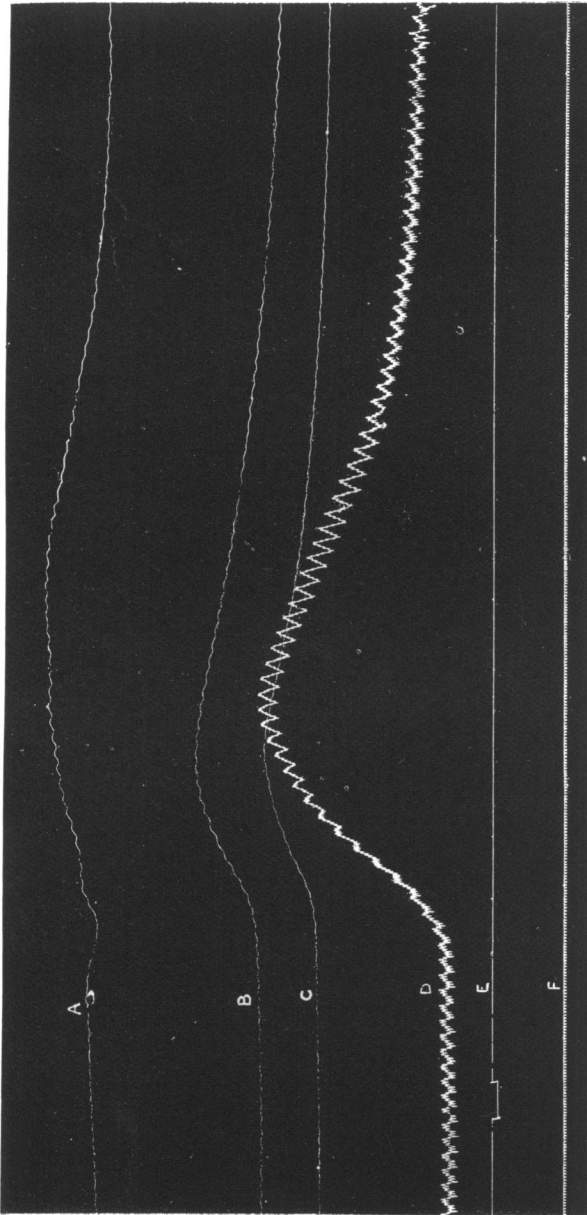Effects of intravenous injection of ·0037 gramme calf-suprarenal (decoction of dried gland).

Fɪɢ. 5. Dog, 19 kilos. Morphia, curare. Artificial respiration. Vagi cut. Cord cut just below bulb. *A*, oncometer tracing of left kidney; *B*, plethysmograph tracing of right forearm (plexus cut); *C*, ditto of left forearm (plexus uncut); *D*, carotid; *E*, abscissa; *F*, time 0·5″.

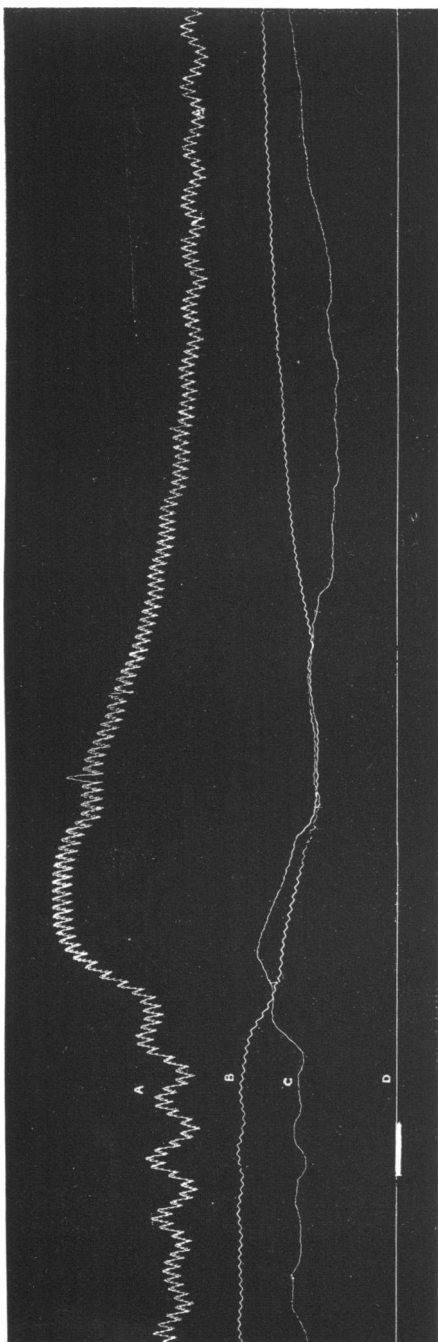Effects of intravenous injection of 0·2 gramme calf suprarenal (water extract).

FIG. 6. Dog, 20 kilos. Morphia, curare (small dose), vagi cut, artificial respiration.

*A*, femoral; *B*, plethysmograph on right forearm, the brachial plexus of which was cut; *C*, plethysmograph on left forearm (brachial plexus intact); *D*, abscissa.

Effect of intravenous injection of a diluted, boiled and filtered glycerine extract of suprarenal = 0·2 gramme (fresh gland).

nution in size of its arterioles, whilst in the latter this active contraction
was more than compensated by a dilatation due to the passive increase
in size of the larger blood vessels.   It was moreover usually found that
in the later stages of experimentation there was a greater tendency to
passive dilatation, especially of the limbs, but also sometimes of the
kidney (fig. 5).   We have not made a large number of experiments upon
the spleen, but in none of them have we got any dilatation except a very
slight preliminary expansion, probably caused by the increased heart's
action, and it may fairly be assumed that although we are unable to
record any plethysmographic observations upon the intestines, the great
rise of blood-pressure which invariably follows the injection of the extract
is in all cases due very largely to the contraction of the arterioles of the
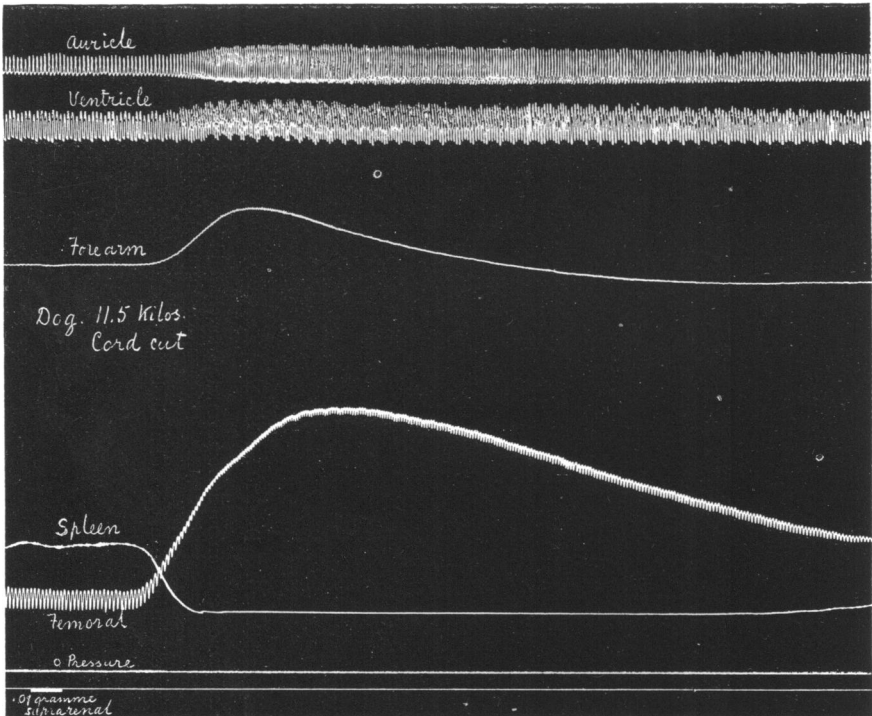splanchnic area.



Fig. 7.   Effects of suprarenal extract upon heart, limb, spleen and blood-pressure,
after section of cord.

In some cases we have noticed in organs enclosed by a plethysmo-
graph an apparent struggle between diminution in size resulting from
contraction of the arterioles and the expansion due to swelling of the

larger blood vessels; and some of our curves show a passive dilatation at the beginning of the effect of an injection followed by a prolonged diminution in size due to a more marked contraction of smaller arteries having supervened (fig. 6 *C*, and fig. 7 (forearm)). That the medium sized arteries also participate in the dilatation is evident from the fact that these always have been found to pour blood out freely from the wounds necessitated by the experiment during the physiological action of the extract injected.

That the contraction of the arterioles is due to the direct action of the active principle of the gland upon the muscular tissue of the blood vessels, is shown by the experiment of perfusing through the blood vessels of the frog already mentioned; it is also demonstrated by the fact that it occurs equally well after section of the spinal cord, and after section of the nerves going to the limb. This is well exemplified in the tracings represented in figs. 8 and 9. In these two figures we record tracings of the blood-pressure and of the alteration in volume of the right and left fore-limbs respectively of a large dog, weighing 20 kilos: the other lines in the tracing being respectively the time intervals and the blood-pressure abscissa. In fig. 6 both limbs are under exactly the same conditions; but in fig. 7 the brachial plexus was cut in the right limb, but left intact in the other. Nevertheless the curves are as nearly as possible similar.

The rise of blood-pressure always occurs after a certain interval of latency. No doubt this interval is mainly occupied by the passage of the extract injected, from the peripheral vein towards the heart, and thence into the arterial system. *Invariably there is a rise of blood-pressure*, never a fall, even temporarily, at the commencement of the injection. We have recorded this latent interval between the commencement of injection of the extract into the vein and the commencement of the rise of blood-pressure in the artery in every case. In the dog it averages 20″. In other animals it is somewhat different; and indeed would naturally vary with the size of the animal and rate of its circulation. The rise of blood-pressure takes place, whether the vagi be cut or not, whether atropine has been injected or not (figs. 1, 2, 3, 4, 5). It is however much greater after section of the vagi or after injection of atropine (figs. 4, 5, 15), because, as will presently be seen, there is usually a concomitant effect upon the cardiac inhibitory centre in the medulla oblongata which tends to produce slowing or stoppage of the auricular contractions. The rise is usually very rapid; sometimes the pen of the kymograph rises almost vertically. In very many cases there is a rapid
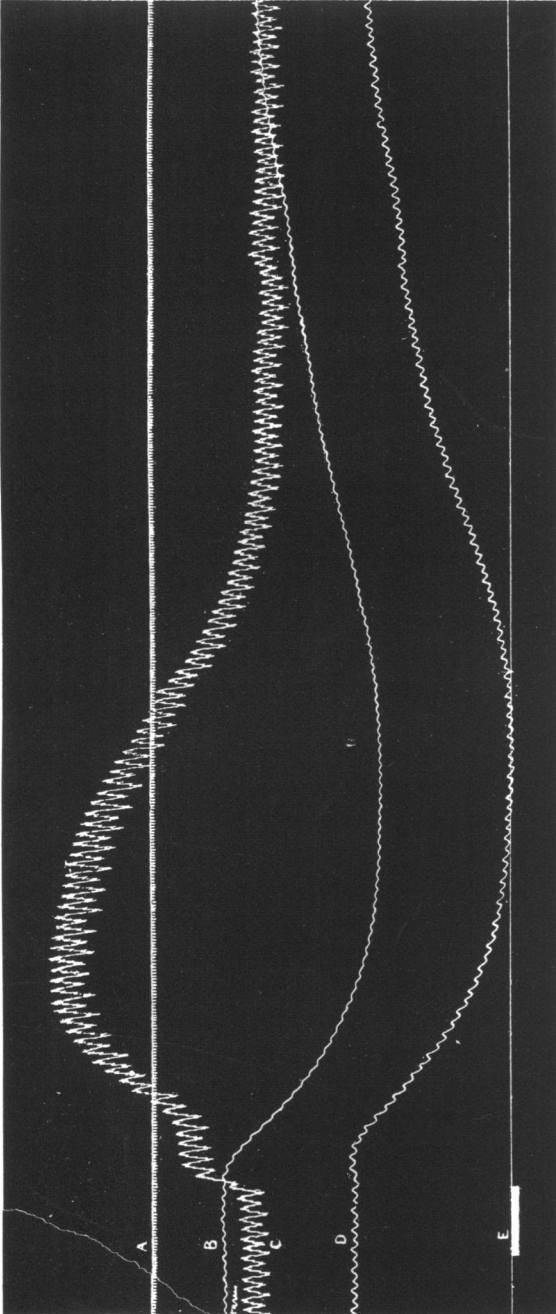
Fig. 8.   Dog, 20 kilos.   Morphia, curare (small dose).   Vagi cut.   Artificial respiration.

*A*, time 0·5″; *B*, plethysmographic tracing of right forearm; *D*, ditto of left forearm; *C*, pressure in left femoral; *E*, abscissa of blood-pressure and place of injection.

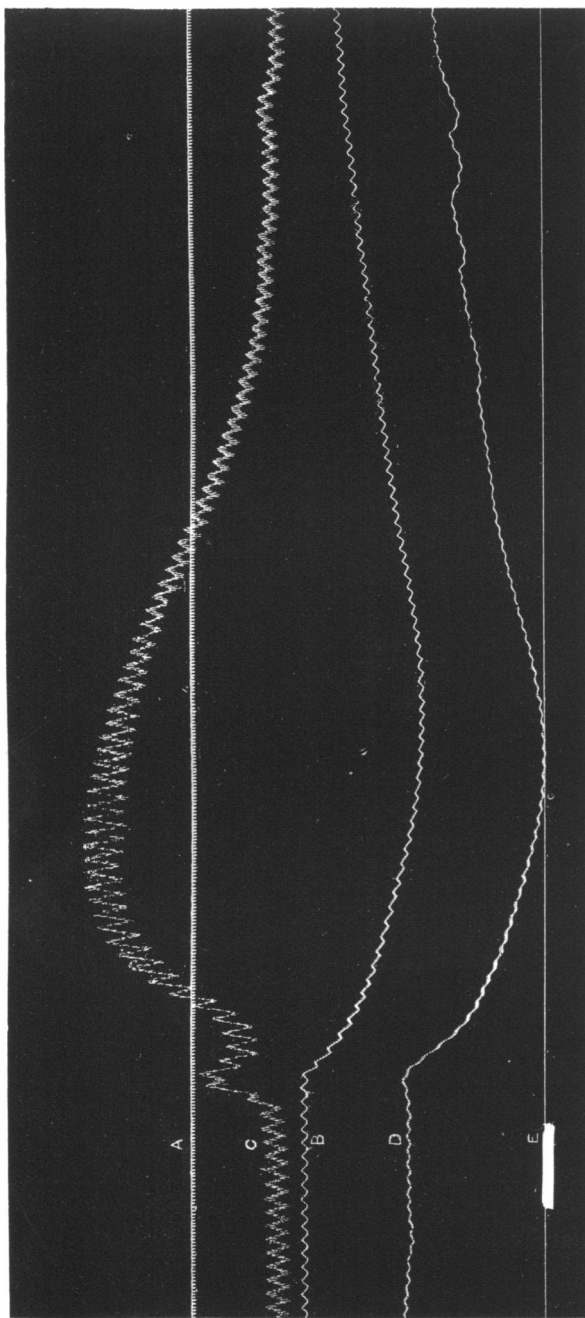Effects of intravenous injection of 0·2 gramme calf-suprarenal (water extract).

FIG. 9.—*A*, time 0·5″; *B*, plethysmographic tracing of right forearm; *D*, ditto of left forearm; *C*, pressure in left femoral; *E*, abscissa of blood-pressure and place of injection.

Between this tracing and that shown in the last figure the right brachial plexus was out by a tight ligature.

Effect of intravenous injection of the same amount of suprarenal extract as in the last tracing.

rise for a few millimetres, followed by a more gradual rise or even in some cases by a slight decline. This however is instantly followed by an even more rapid rise than the first. The blood-pressure may in this way mount up, especially after previous section of the vagi or the administration of atropine to a height of from 2 to 5 times or more that which it had originally (figs. 4, 5, 15, 16): indeed, even although we have employed an exceptionally long manometer, in more than one instance the mercury has been entirely driven out from the open end of the tube. This rise of blood-pressure after section of the vagi or after administration of atropine is not entirely due to the action of the drug upon the blood vessels, it is also, as will presently be seen, largely augmented by the increased action of the heart. The blood-pressure having risen to a maximum height is maintained for a certain number of seconds nearly at the same level. But before long it begins gradually to fall, and after a variable time, depending partly upon the animal employed, partly upon the amount and potency of the extract employed, it is found to have regained the normal level. The longest time that we have found the action of the extract upon the blood-pressure to be prolonged as the result of one dose has been 4 minutes in the case of the dog (weight 20 kilos, dose 0·19 gramme), and 6 minutes in the case of the rabbit (dose 0·096 gramme). But if the extract is allowed to flow slowly but continuously into the vein the pressure is kept up as long as the flow is continued, and for the usual time after it is discontinued. There may sometimes be seen upon the course of the declining curve one or two irregularities, but we have generally found that these are produced either by an occasional explosive respiration or by a struggle. As a rule the decline of the curve is gradual with a slight dip towards the abscissa. During the whole period of the elevated blood-pressure caused by the injection of the extract the Traube-Hering curves are usually abolished (fig. 10), to appear again at the close of the effect of the injection (provided that they have been apparent before the injection was made). We have further ascertained, both in the cat and in the rabbit, that during the whole period of the rise of blood-pressure resulting from suprarenal injection the effect of central stimulation of the depressor nerve is altogether in abeyance; as the blood-pressure approaches the normal, slight depressor effects are obtained; and when the normal blood-pressure is reached the full effect of depressor stimulation is again manifested (fig. 11, I. and II.).

Finally it may be noted as the result of the obstruction due to the contraction of the arterioles and the great rise of venous, and hence of
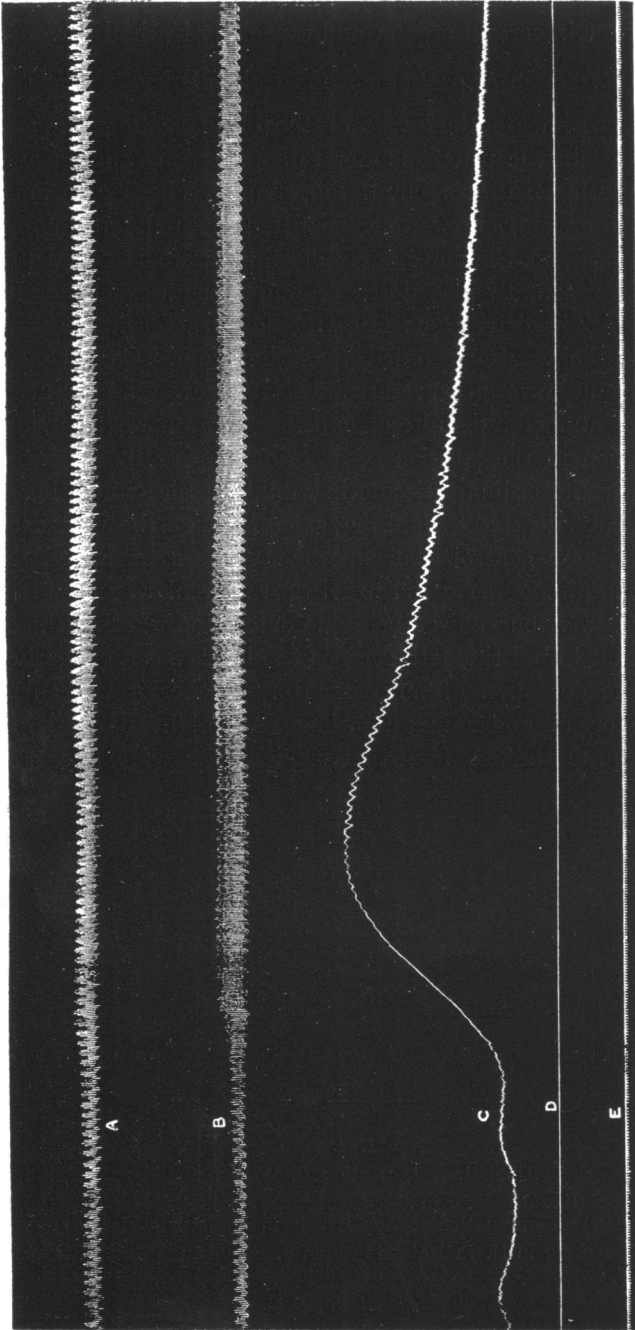
FIG. 10. Dog, weight 9 kilos. Morphia in excess. Vagi cut. Artificial respiration.

*A*, ventricle; *B*, auricle; *C*, femoral; *D*, abscissa of blood-pressure (the injection of suprarenal occurred just before *D*); *E*, time in 0·5″.

Effect of intravenous injection of decoction of 0·2 gramme dog-suprarenal with very low blood-pressure. Abolition of Traube-curves.

capillary pressure which may thereby supervene, extravasations of blood are liable to occur in certain organs, and especially in the liver.

### (c)   Effects of the extracts upon the isolated frog-ventricle.

In these experiments the heart of the ordinary frog (Rana temporaria) was tied in the usual manner to a perfusion cannula and fed through this with Ringer's circulating fluid.   The expansion and contraction of the ventricle were transmitted through oil to a horizontally moving piston, the movements of which were recorded upon a slowly moving horizontally placed drum*, and gave an exact measure of the amount of fluid driven out from the heart at each contraction; time in seconds being also recorded upon the drum.   Connected with the perfusion cannula were two reservoirs of Ringer's circulating fluid, one of which contained a definite amount of suprarenal extract, and by a slight alteration in the position of a spring clip or by the use of a 3-way tap either the ordinary circulating fluid, or the circulating fluid containing suprarenal extract could be passed through the ventricle.

In one case, as a control, the experiment was so arranged that a decoction of frog-muscle was added to Ringer's circulating fluid instead of suprarenal extract, our object being to determine whether the effect which was obtained from the extract upon the heart was a general effect produced by the decoction of any tissue or whether it was an effect special to the organ under investigation.   As might be anticipated, the result was quite different from that yielded by suprarenal extract.
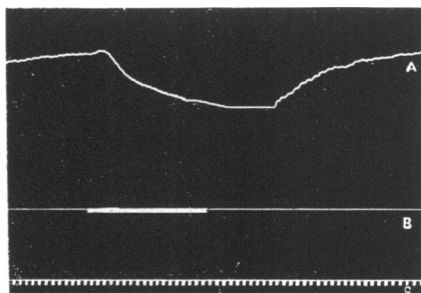


Fig. 11. I.

FIG. 11.   Large rabbit.   Chloral.   A, carotid; B, abscissa and signal; C, time 1″.

I.   Effect of stimulating depressor in absence of suprarenal.
II.   Absence of effect on stimulation of depressor during suprarenal rise of pressure.

The first signal marking in II. indicates injection of extract, the numbered markings indicate excitation of depressor nerve.   At 10 the depressor effect has re-appeared.
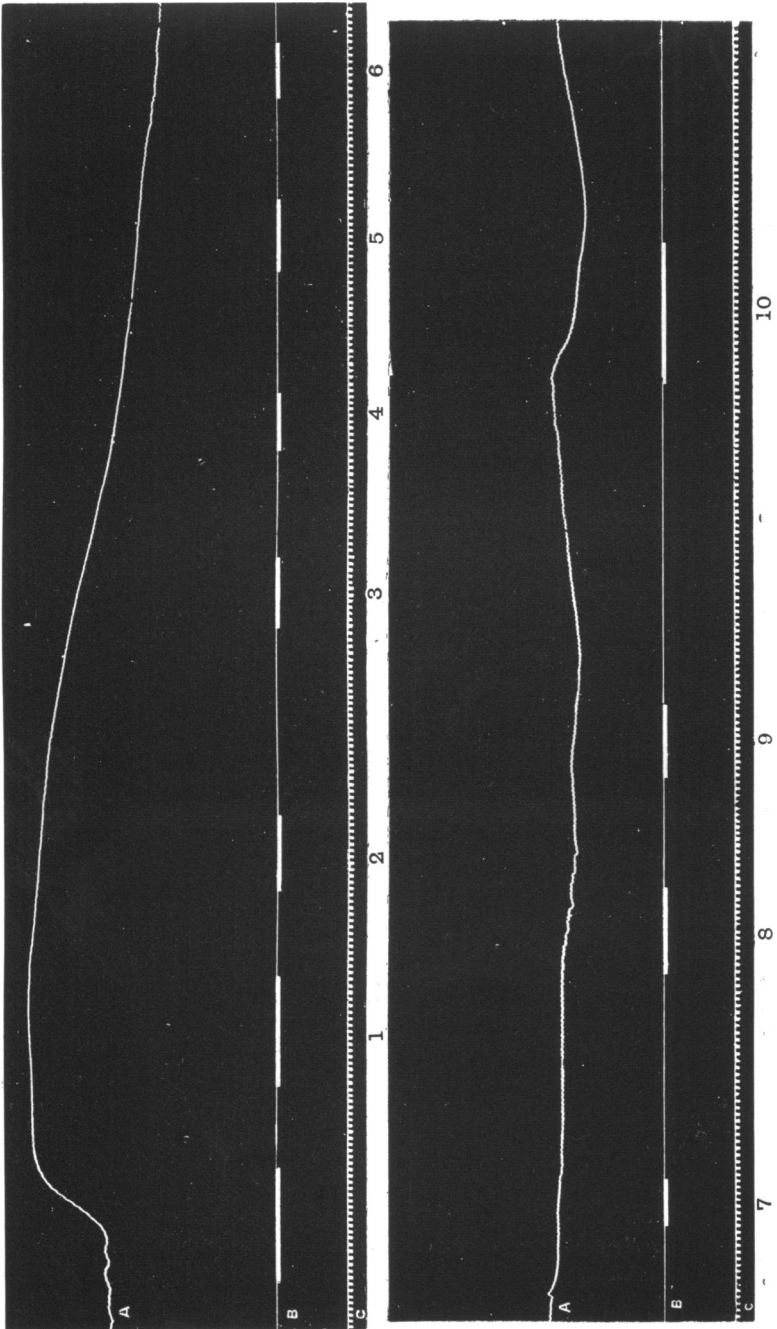
* This Journal, v. p. 130.

Fig. 11. II.

The general results which we have obtained from observations upon the isolated ventricle under different conditions of its activity may be briefly stated as follows:

(1)   When the rhythm of the isolated ventricle is imperfect.   When a frog's heart is perfused with a saline solution, such as Ringer's circulating fluid, it is not uncommon (especially at the beginning of the experiment, but sometimes during a prolonged period) for the rhythm of the ventricle to be imperfect, so that either (a) it does not beat spontaneously at all, or (b) its contractions only recur after long intervals of time, or (c) its beats manifest Luciani's groups, all of which are probably signs either of temporary malnutrition or of lack of sufficient excitation for the production of the regular rhythmic beat.   The first effect which the addition of suprarenal extract to the circulating fluid invariably produces is in the case of (a) to produce spontaneous contractions, of (b) to accelerate the rhythm, of (c) to lengthen the groups, that is to say, to increase the number of beats in each group. Very soon the contractions in all cases become regular, and in the last case there is soon apparent a tendency to abolish the grouping altogether and to cause the rhythm to be uniform (fig. 12 A).

(2)   Suprarenal extract if perfused through a heart which is beating feebly appears to have a tendency to increase the strength of the contractions.   This is however a point which we cannot speak very positively about, because in most of our experiments the heart-beat was at its maximum of force with the Ringer's solution alone.   It abolishes the " staircase " in Luciani's groups.

With a certain proportion of suprarenal extract an effect which is well-marked is the reduction in the time of the pause between two successive heart-beats, so that with a certain strength of the solution the pause may be entirely obliterated, and the beats succeed one another without any apparent interval.

A further stage in this action, which obtains with solutions of still greater strength (1 p.c. and upwards), is that the beats begin to run the one into the other, one contraction succeeding another before the completion of the preceding diastole.   The result is that the dilatation is imperfect, and may ultimately be almost entirely or quite obliterated, so that eventually the heart stops in systole (fig. 12 B).   If however the circulating fluid containing suprarenal extract be now washed away with ordinary circulating fluid the heart may completely recover, and the experiment may be repeated two or three times in the same fashion.

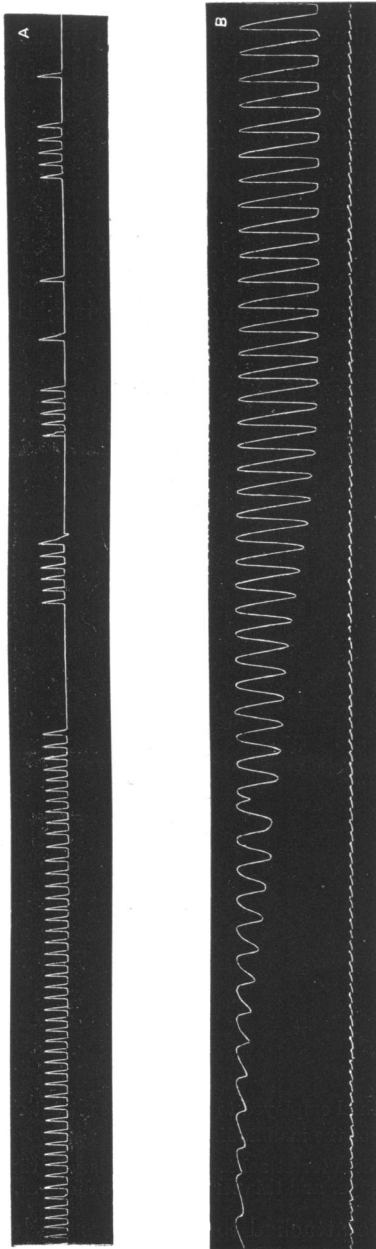Our results with the frog-heart as compared with that of the

Fig. 12. To be read from left to right.

A, effect of a small dose in abolishing Luciani's groups. B (another heart). Effect of a larger dose in abolishing the diastolic phase.

Effects of water extract of suprarenal on isolated frog-ventricle, fed with Ringer's circulating fluid.

mammal show that relatively larger doses are required to produce a
marked effect, and a similar statement will apply also to the results
obtained with the blood vessels and skeletal muscles of the frog.

### (d)  *Effects on the mammalian heart.*

In this series of experiments the muscular contraction of each part
of the heart has been inscribed graphically in the following manner
(fig. 13): a fine steel hook is caught in the epicardium of the auricle,
and another in that of the ventricle; from these hooks fine cotton
threads pass first over pulleys moving on a horizontal axis, and then
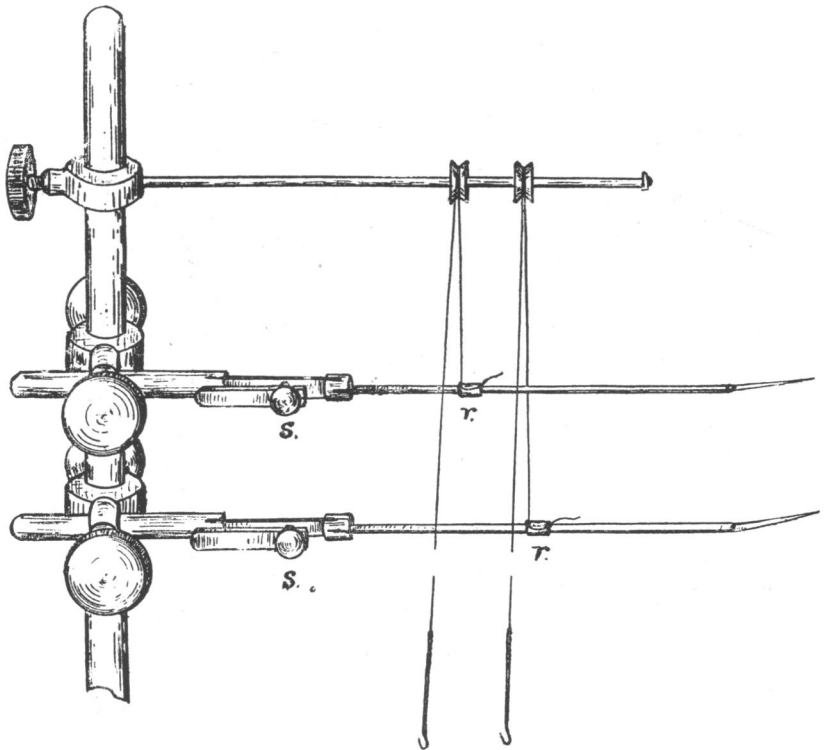


Fɪɢ. 13.    Diagram of method employed to record the contractions of the parts
of the mammalian heart.

*s, s,* adjusting screws ; *r, r,* riders for attachment of threads.  In the apparatus actually
used the steel levers are much longer and thinner than in the diagram.

vertically downwards, to be attached to long levers made of flat springy
steel.   To the ends of the levers writing pens are attached; and the
lever is so constructed that it yields to the least pull of the thread.   In

order that the pull of the ventricle shall not affect directly the thread which is attached to the auricle, a metallic ring is passed through the aperture made in the thorax to expose the heart, and into the pericardial cavity between the auricle and ventricle; those of the right side of the heart having generally been used. This ring serves sufficiently to fix the base, and to prevent the action of the one part from directly affecting the lever which is connected with the other. Sometimes in place of using this ring, the base of the ventricle, at the auriculo-ventricular boundary, has been held firmly by a clip.

The extracts were administered by intravenous injection, and the contractions of the auricle and ventricle were invariably recorded at the same time as the blood-pressure, and in some cases also at the same time as the plethysmographic observation of one or more organs. These experiments like those upon the blood-pressure have been performed upon dogs, cats and rabbits, but by far the greater number upon dogs.

Firstly, it may be remarked that the effect which extract of suprarenal produces upon the heart is entirely different according to whether it is observed with the vagi intact or with the vagi cut or paralysed by atropine. When one or both vagi are intact and the animal is under chloroform only, or under chloroform in conjunction with morphia, the most striking effect upon the heart is the inhibition of the auricles. Their action, after the period of latency necessary for the passage of the solution to the heart, is rapidly stopped in diastole, in other words, they are powerfully inhibited. But usually this inhibition of the auricle is preceded by a short period of augmentation.

In one or two cases the primary period of augmentation has been prolonged for two or three minutes. But even in these cases, provided the vagi are intact, the inhibition ultimately succeeds it, the vagus action having been only deferred until after a period of augmentation and acceleration (compare fig. 14 with figs. 15 and 16). As in most other cases where the auricle is caused to stop by vagus action, the ventricle immediately recommences beating but with an altered rhythm; a rhythm which is invariably slower than before. This is well exemplified in fig. 14, which shows in the top line the tracing of the ventricle, in the second that of the auricle, in the third that of the blood-pressure, and in the other lines the blood-pressure abscissa and the time in half-seconds. The deferring of the inhibitory action which sometimes occurs is shown characteristically in fig. 15 and fig. 1.

The inhibitory action of suprarenal extract is not a direct action upon the heart. That this is so is evidenced by the fact that after
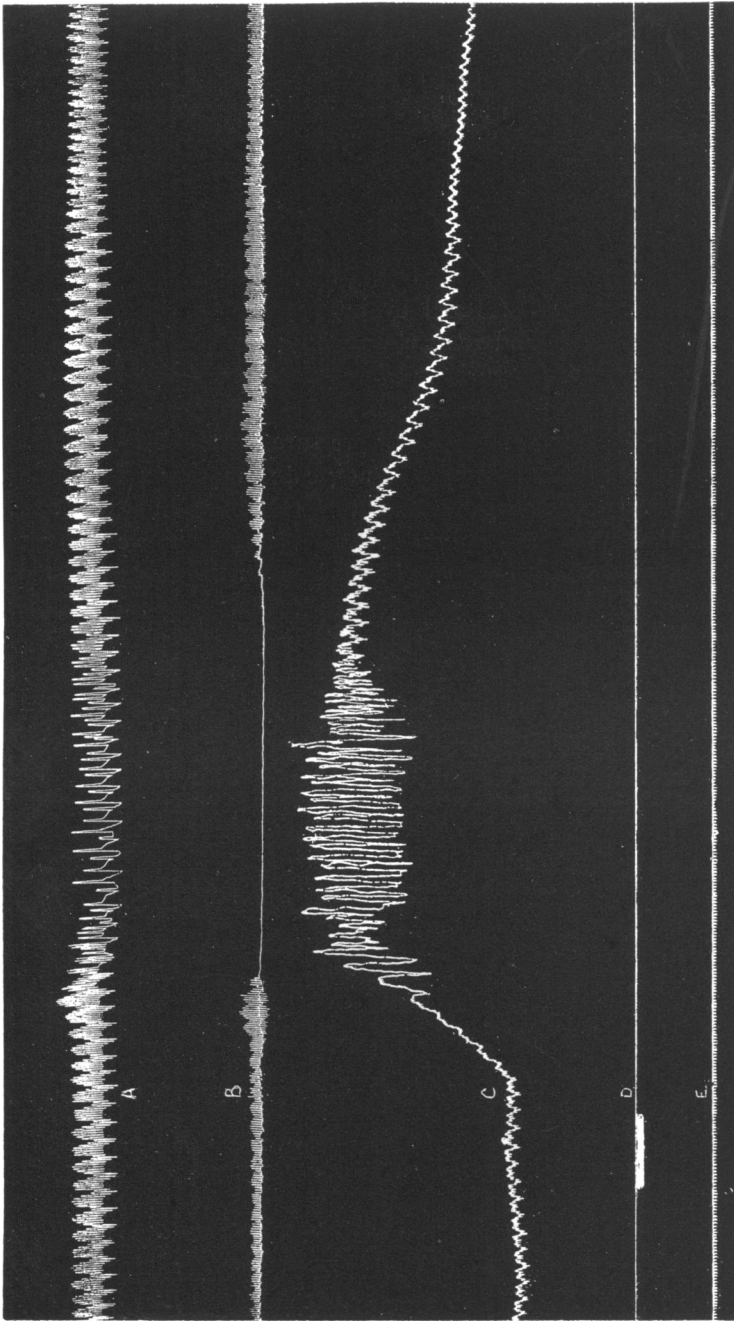
Fig. 14. Dog of 9 kilos. Morphia. Artificial respiration. One vagus cut. *A*, ventricle; *B*, auricle; *C*, femoral; *D*, abscissa of blood-pressure; *E*, time 0·5″. To left of *D*, intravenous injection of decoction of 0·2 gramme dog-suprarenal.
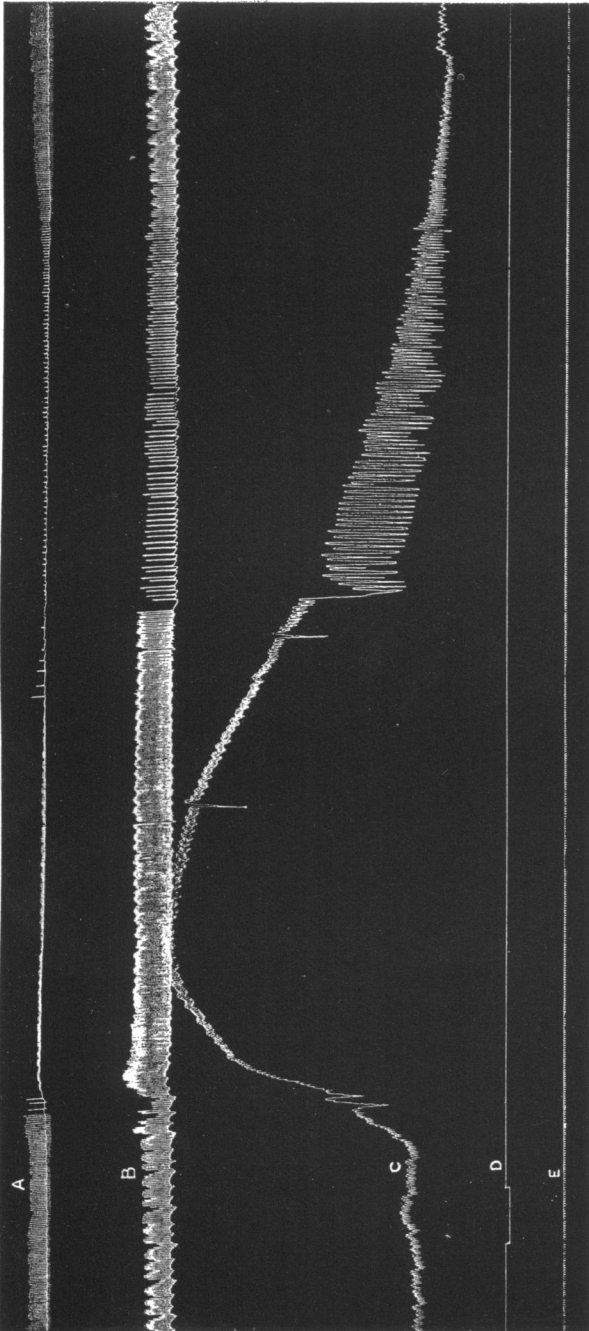
FIG. 15.   Dog of 16 kilos.   Morphia.   Vagi uncut.

*A*, auricle; *B*, ventricle; *C*, femoral; *D*, abscissa of blood-pressure and mark of injection; *E*, time 0·5″.

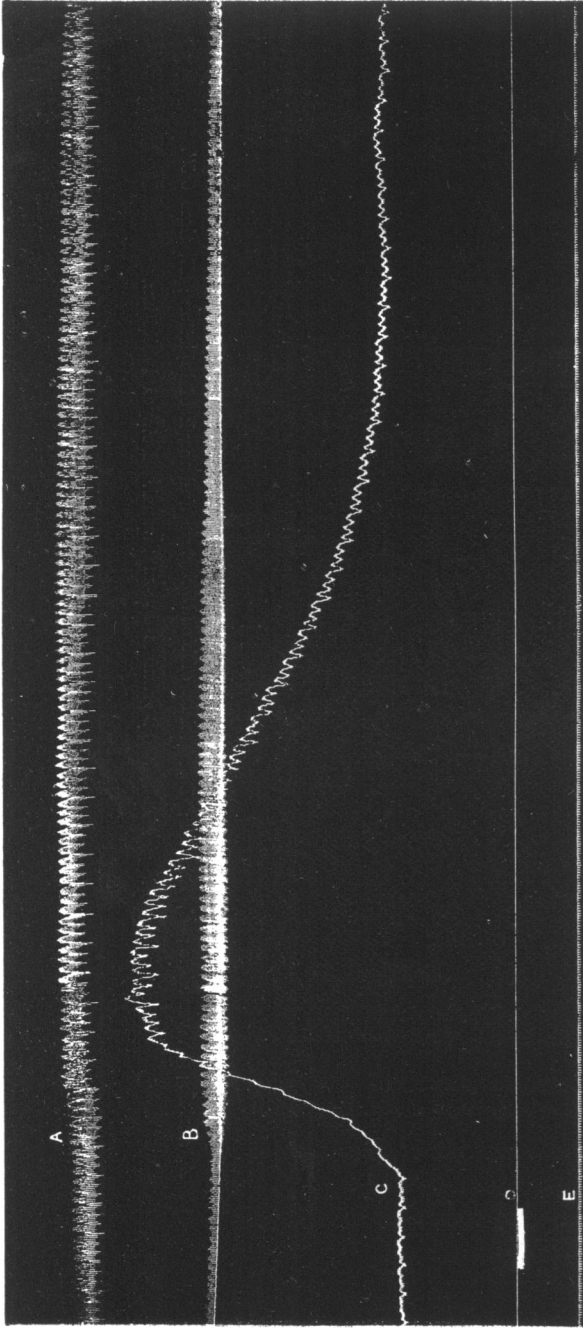Effect of injecting extract of 0·2 gramme dog-suprarenal.   Delayed inhibition.

FIG. 16.   Dog, 9 kilos.  Morphia.  Artificial respiration.  Vagi cut.

A, ventricle; B, auricle; C, carotid; D, abscissa and signal; E, time 0·5″.

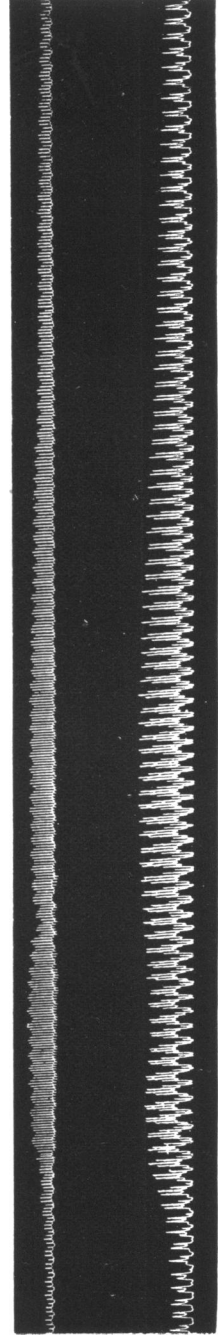Effect of intravenous injection of about 0·2 gramme suprarenal (spirit extract).



FIG. 17.   Tracing of effect of intravenous extract upon the auricle (upper curve) and ventricle respectively of a large dog.
Morphia, atropine, curare, cord cut.

destruction of the medulla oblongata, after section of the vagi (fig. 16), or after the administration of even a small dose of atropine (many figures) the inhibition entirely disappears. The effect which is then obtained is invariably augmentation and acceleration; a well-marked increase in the force and frequency of the auricular beats accompanied by a similar increase in force and frequency of the contractions of the ventricle. This increase in force may be so great in the case of the auricle that the excursion of the lever is four or five times its original amount (fig. 17). The effect lasts as a rule as long as the elevation of the blood-pressure, apparently therefore as long as the contraction of
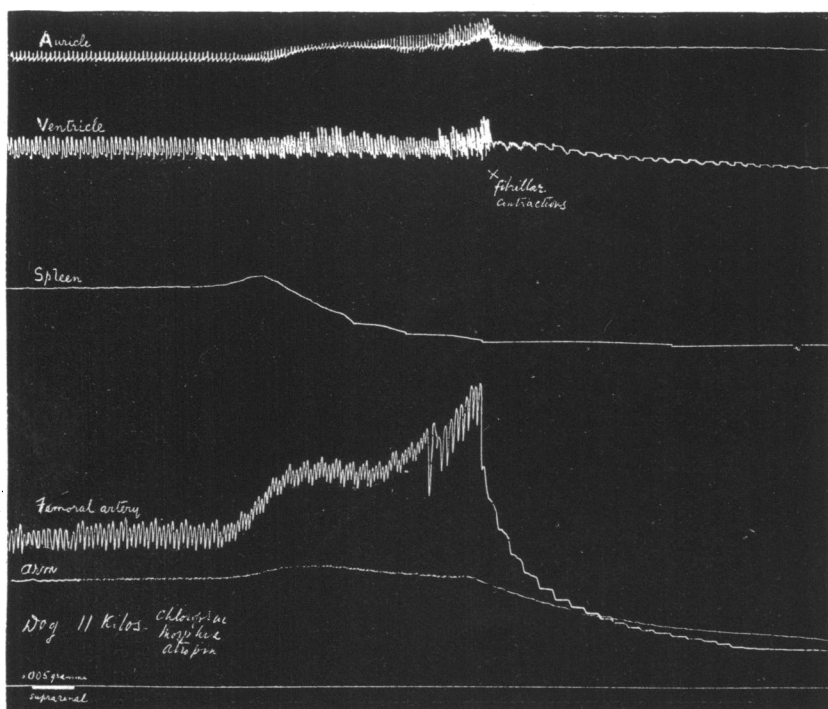


FIG. 18. At × fibrillar contraction of ventricle, caused by suprarenal extract. The curves beyond this are caused by the artificial respiration.

the arterioles; remaining at a maximum for a certain period, and after this gradually declining. It is usually followed by an after-effect, in which the force and frequency of the heart's beats are both somewhat diminished.

In a single experiment, one of very many which we have performed,

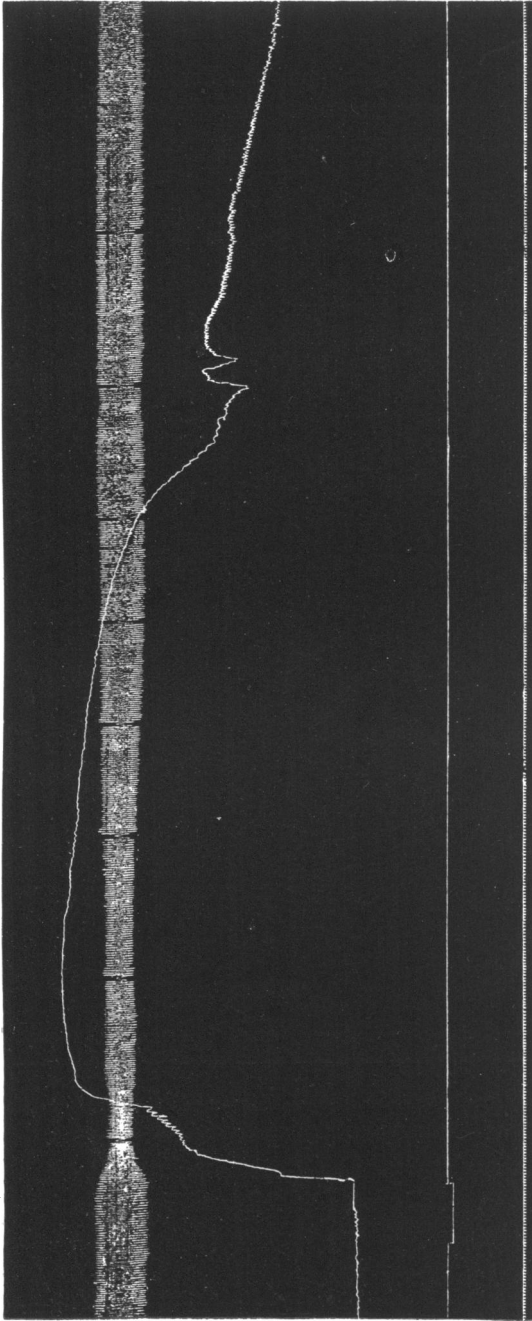FIG. 19.  Large rabbit anæsthetized with chloral.

The upper tracing shows the effect upon the respirations, which were recorded by a tambour connected with the tracheal tube; the second tracing the blood-pressure (carotid); the third line the blood-pressure abscissa and the place of injection, and the fourth line time in 0·5″.

Effect of intravenous injection of 0·065 gramme calf-suprarenal (water extract)

the intravenous injection of the extract began by producing the ordinary effects upon the circulating system.    At the moment however when the blood-pressure had attained its full height the ventricle passed into a condition of fibrillar contraction from which it failed to recover.    The tracing of this experiment is given in fig. 18.

### (e)   Effect on the Respiration.

We have investigated the effects on the respiration in the rabbit and in the dog.   Similar results are obtained in both, but the effect is most marked in the rabbit.   It occurs for the most part soon after the administration of the drug, and may result in arrest of respiratory movements for a short time.    More commonly, however, there is produced a shallowing of the respirations, which persists for a certain period and then gradually passes off (fig. 19).   In the dog no stoppage of respiration was ever obtained, but the respirations although proceeding with an ordinary rhythm were for a few times slightly shallower.

### (f)   Effect on the Skeletal Muscles.

The effect of subcutaneous injection of suprarenal extract upon the voluntary muscular contractions of the frog have already been noted (p. 239); we have further also made a graphic record of the effect of the drug upon the muscle-curve.   This effect is well exemplified in fig. 20, in which A is a normal muscle curve from an unpoisoned gastrocnemius of a frog, and B is the result of a similar stimulation of the poisoned muscle.   It will be seen that in both cases the period of latency is about the same, and that the height of the curve is nearly similar, but that the curve is greatly prolonged in the case of the muscle which has been acted upon with suprarenal extract.   In the dog we have made similar observations, recording upon a myograph the contraction of one of the forearm muscles, which was stimulated through its nerve by a single induction shock before and after suprarenal extract was injected into a vein.   This gave results quite similar to those obtained in the frog.   The normal curve is prolonged; but the period of latency is not increased.   The effect is not a fatigue effect, but is comparable rather to the effect of a slight dose of veratria. Moreover we found the effect upon the muscular system of the dog to remain long after the result of the action of the extract upon the heart and blood vessels had disappeared.   We think it, therefore, possible

that the extract after it is injected into the blood may be taken up into the muscular system, and that this may account for the gradual disappearance of its action upon the other organs. It is needless to say in
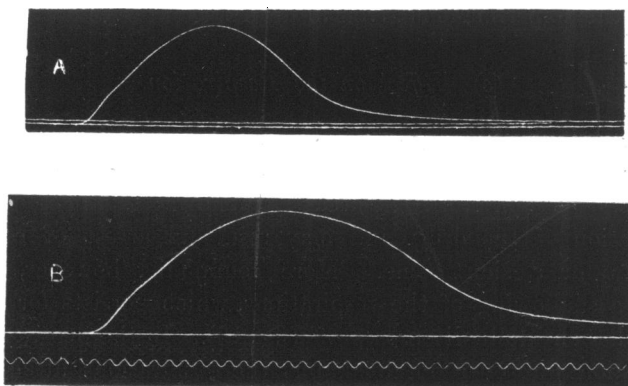


FIG. 20. Effect of suprarenal extract upon muscle contraction in the frog.

A, normal muscle-curve of gastrocnemius; B, curve taken during suprarenal poisoning, but otherwise under the same conditions as A. Time 0·01″.

view of the curves which we give that the effect is in no way comparable to that of curare, for the muscle reacts through its nerve, just as powerfully or even more powerfully than before to the same stimulus, and not only is the contraction not diminished, but it is greatly maintained, the period of relaxation being vastly prolonged.

## (g) Effect on Secretory Glands.

We have investigated the effect of suprarenal extract upon the secretion of the submaxillary gland, and upon the nervous mechanism of that gland. Without entering into details of the methods employed, which were precisely the same as those which have been used by all workers on the subject of the secretion of that gland, we may state briefly that we have not found any difference in the amount of secretion of the gland to result from suprarenal extract, either when it is secreting spontaneously or during excitation of its nerves. In spite of the extensive contraction of the arterioles produced by the extract, stimulation of the chorda produces as free a secretion as usual.

IV. The Physiological Effects of Suprarenal Extract com-
pared with those of certain other drugs which are
known to influence the heart and blood vessels.

We have thought it of interest to compare the physiological effects
upon the heart and arteries of suprarenal extract with those of certain
substances known to influence those organs, and especially digitalis,
ergot, and neurin. We have used for this purpose freshly prepared
decoction of digitalis leaves, liquid extract of ergot and various solu-
tions of neurin and compounds of neurin, especially phosphate and
glycerine-phosphate. We were led to investigate the action of neurin
chiefly from the fact that certain observers have stated that the
physiological results obtainable from extract of suprarenal capsules are
due entirely to the neurin which they contain.

1. *Digitalis and Ergot.* With comparatively large doses of
digitalis (a freshly prepared extract from 0·22 grammes of the leaf in a
dog weighing 7·7 kilos injected into a vein) hardly perceptible effects
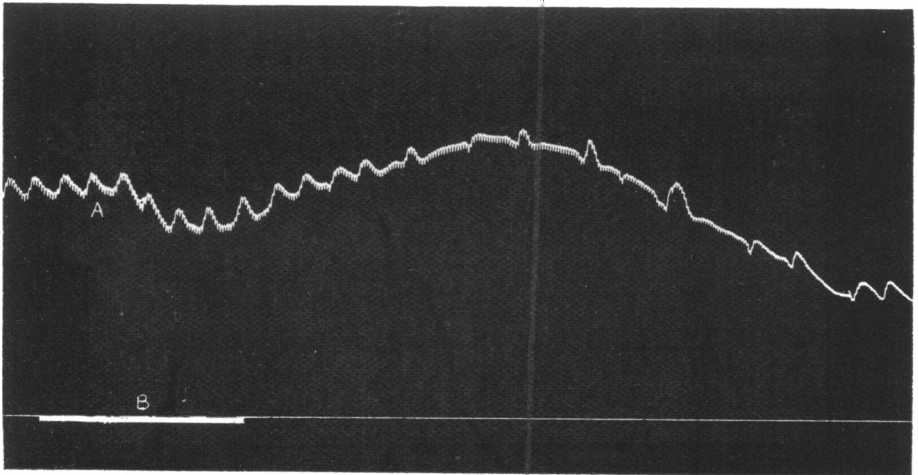were obtained upon the blood-pressure, whereas in the same dog the



Fig. 21. Dog, 6·3 kilos. Morphia, atropine.
At *B* intravenous injection of ergot.

administration of an extract containing the active substance of
0·01 gramme of suprarenal caused the blood-pressure to rise two to
three times its original height. With ergot we have also got very
insignificant results. The dose which we used was the extract of

1·5 grammes of the powdered drug and the effect of an injection of this dose into a dog weighing 6·3 kilogrammes is shown in fig. 21. The effect upon the blood-pressure of an injection of 0·06 gramme of suprarenal extract into the same dog was enormous.

2. *Neurin.* We have used preparations of neurin made for us from yolk of egg by Mr B. Moore of this laboratory, and also a preparation obtained from Kahlbaum. We have employed, besides the base itself, the phosphate and glycero-phosphate and also the hydrochlorate of neurin. It has been stated by Marino-Zucco that the toxic effects
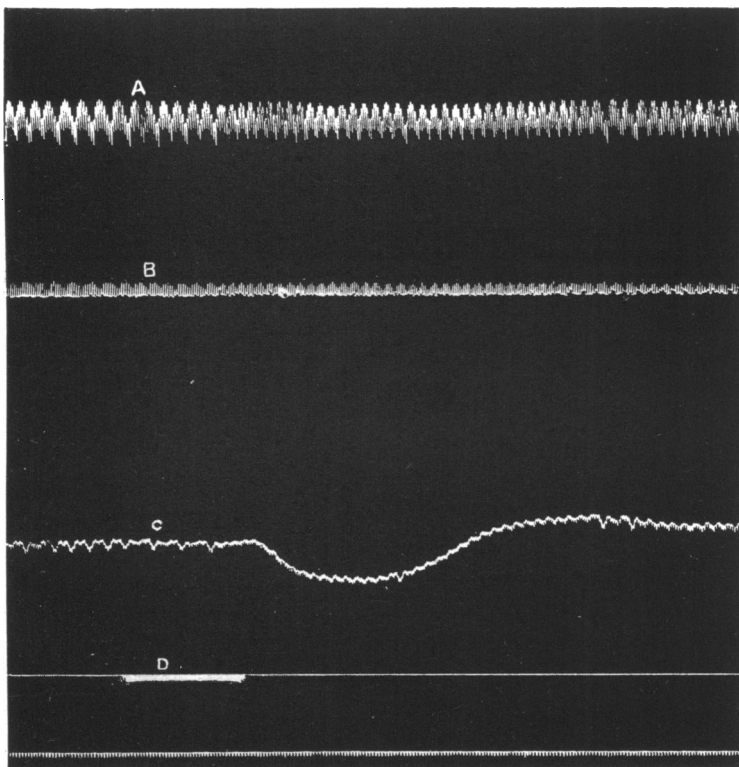


FIG. 22. Dog, 9 kilos. Morphia. Artificial respiration. Vagi cut.
*A*, ventricle; *B*, auricle; *C*, carotid. Time 0·5″; *D*, intravenous injection of neurin.

which are obtained from extract of suprarenal capsule are due rather to these salts of neurin than to the base itself in an uncombined form: we . have however obtained similar results from all, results in no way similar to those yielded by suprarenal extract. Fig. 22 shows the effect of the injection of a solution of neurin into the circulation of a

dog weighing 9·09 kilogrammes. It will be seen that the result is entirely different from that which suprarenal extract produces. Indeed one of the most marked features of the curve is a preliminary fall in the blood-pressure, and although this is succeeded by a slight rise, the latter is again speedily replaced by a permanent depression.

Cervello[12], who has written an extensive article upon the physiological effects of neurin, and gives the results of experiments upon the blood-pressure, found that the neurin which he employed produced a certain rise of blood-pressure. For example, before section of the vagi a rise of blood-pressure was produced by the dog of from 156 mm. to 262 mm. (maximum), and after section of the vagi from 168 mm. to 264 mm., under both circumstances the heart was slowed. The doses employed were large, and the results obtained are perfectly insignificant compared with those yielded by the minute doses of suprarenal extract which we have used ; the amount of neurin which these doses of extract contain must be absolutely imperceptible. Moreover the effects obtained by Cervello as the result of the action of neurin upon secretion, upon the heart and upon the muscles are all entirely different from those produced by suprarenal extract. We conclude therefore that the effects resulting from injection of this extract are not due to any neurin that it contains, and it will be obvious by a glance at the tracings that the effects produced both upon the heart and blood vessels are vastly different and more potent than those of even such drugs as digitalis and ergot, which have a widespread reputation for increasing the contractions of the muscular tissue of the heart and blood vessels.

## V. IS THE ACTIVE PRINCIPLE OF THE GLAND CONTAINED IN THE CORTEX OR IN THE MEDULLA ?

We have investigated the comparative activity of extracts prepared respectively from the cortical and medullary portions of the suprarenal bodies. In order to avoid as much as possible any contamination of the one part of the gland with the other we have frozen the glands, and having first sliced away portions of the cortex and prepared these, have then proceeded deeper until we came to the medulla. On arriving at the medulla we have sliced away the cortex from the sides also and then were able to prepare portions containing medulla alone. The extracts of both cortex and medulla were made by boiling weighed portions for a few minutes in salt solution and precisely the same
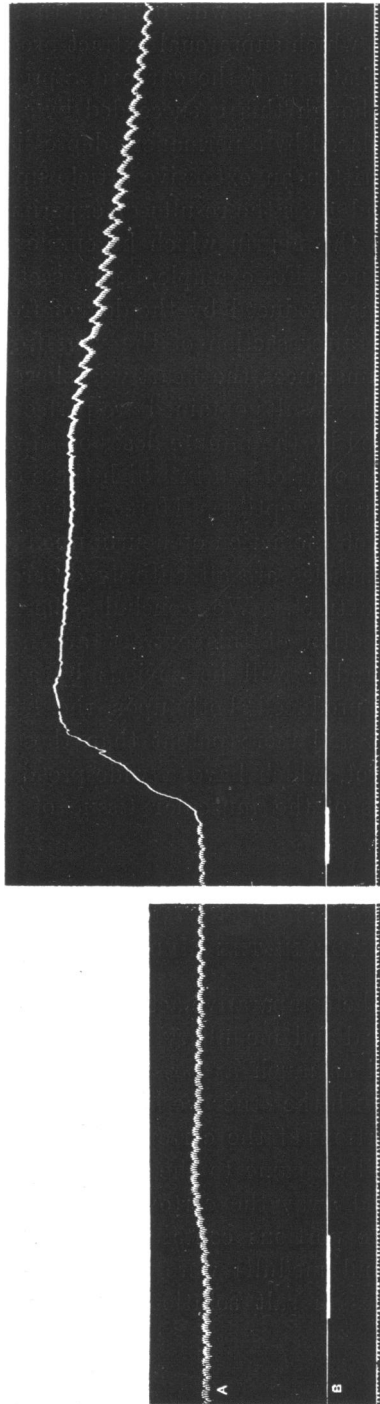
Fig. 23. Large dog. Morphia, atropine.

Effects on the blood-pressure of intravenous injection of similar doses of decoction of I. cortex, and II. medulla of suprarenal gland of calf.

proportions of gland to salt solution were used in each case. The results of these experiments are quite decisive. Injection of a large dose of extract of the cortical substance has little or no effect, whereas extract of even a minute dose of decoction of the medullary substance produces the ordinary physiological results to a prodigious degree (fig. 23).

We conclude therefore that the active principle of the extract is contained entirely in the medulla, the very small effects which we have sometimes got from extracts of cortex being probably to be explained by post-mortem diffusion of the medullary juice, or other accidental contamination.

## VI. The Effect of Extract of Diseased Suprarenals
(Addison's disease).

We have investigated the effects of dilute alcoholic and watery extracts of suprarenals which were extensively diseased (Addison's disease), and microscopical examination of which showed complete
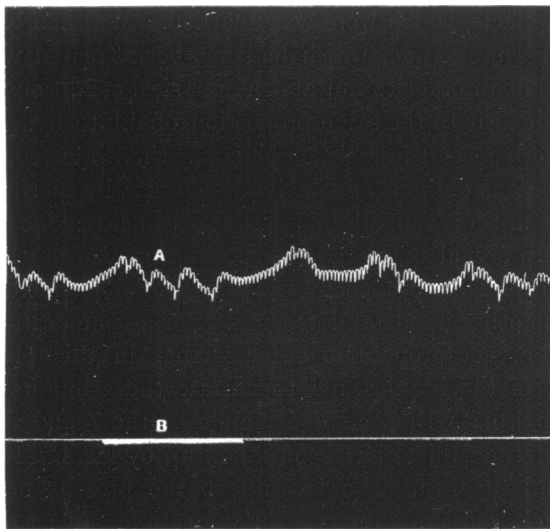


Fig. 24. Dog, 5·5 kilos. Morphia, atropine.
*A*, femoral; *B*, abscissa of blood-pressure and signal of intravenous injection of extract of Addison suprarenal.

caseation of the medulla and a sclerosed condition of the cortex. These produced no effects when injected into the blood vessels of dogs. We

conclude therefore that in advanced Addison's disease the physio-
logically active substance of the suprarenal capsule is no longer pro-
duced (compare the tracing in fig. 24 with those in figs. 25 and 26).

VII.  THE EFFECTS OF HEAT, ACIDS, ALKALIS, AND PEPTIC DIGES-
      TION ON THE ACTIVE PRINCIPLE OF SUPRARENAL EXTRACT.

As will be seen from what we have already said the temperature of
boiling water produces no effect upon the physiologically active principle;
but if the boiling is prolonged for some hours the activity gradually
diminishes, and may ultimately disappear.  The active principle does
not however distil over.  Dilute acids, even mineral acids, appear to
have no effect in altering the activity of the gland, and the same remark
applies to the combination of hydrochloric acid and pepsine which is
met with in artificial gastric juice.  In order to test this we took a
portion of active suprarenal extract and digested it for 24 hours in an
active artificial gastric juice at the temperature of the body.  Some of
this acid solution we injected into the veins of a dog, and noted the
physiological effects, which were very marked.  We then took a similar
portion of the same extract which had not been treated with artificial
gastric juice, but in order to imitate the physical conditions as nearly as
possible we added it to the same proportion of dilute hydrochloric acid
as that used for the first injection.  This was then injected, and a result
exactly similar was obtained.  Finally as a control experiment we took
a similar amount of the dilute hydrochloric acid alone without the
addition of suprarenal extract, and injected this also at the same rate
into the vein.  This produced no perceptible physiological effect.
Alkalis, on the other hand, diminish, and after a time destroy the effect.
We do not however propose to enter further in this place into the
chemical part of the inquiry, nor to narrate the attempts which have
been made to isolate the active principle of the gland extract, since
this portion of the subject has been taken up by Mr B. Moore, of this
laboratory, and the results he has up to the present obtained have
been published in a preliminary communication made to the Physio-
logical Society in March 1895 and already published in this *Journal.*

Suffice it to say that the active principle appears to be identical
with a substance which was first obtained by Vulpian[13] from the
medulla of the gland, and the solutions of which assume a rose-red
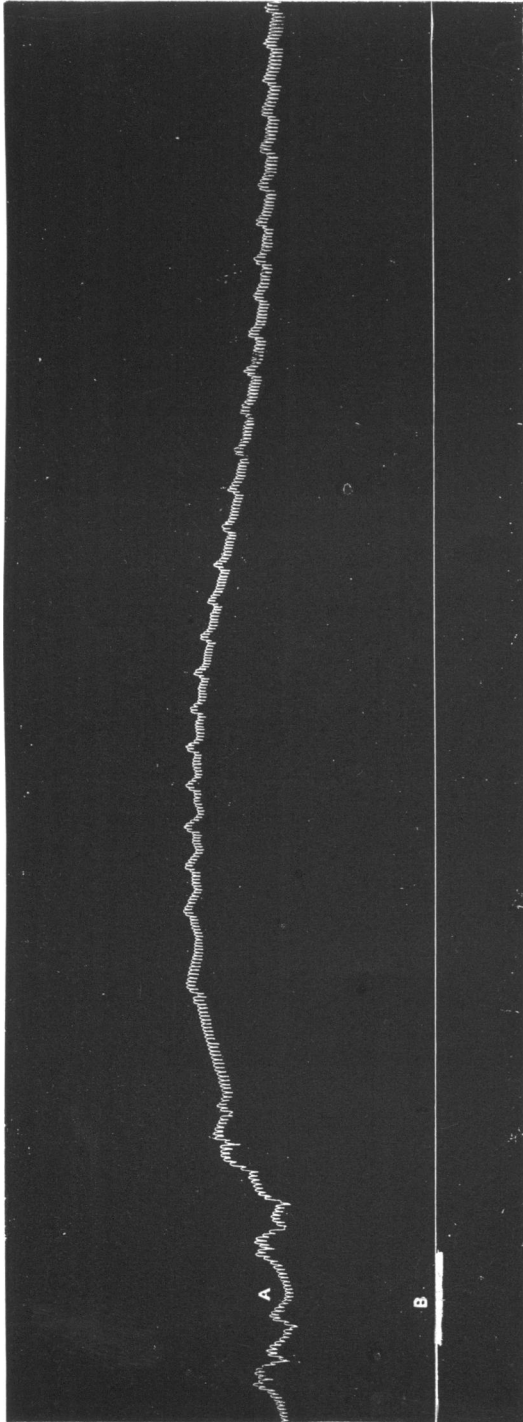colour on exposure to the air or to oxidizing reagents.

FIG. 25. Dog, 5·5 kilos. Same as last figure, but extract of normal human suprarenal (minimal dose) employed for intravenous injection.
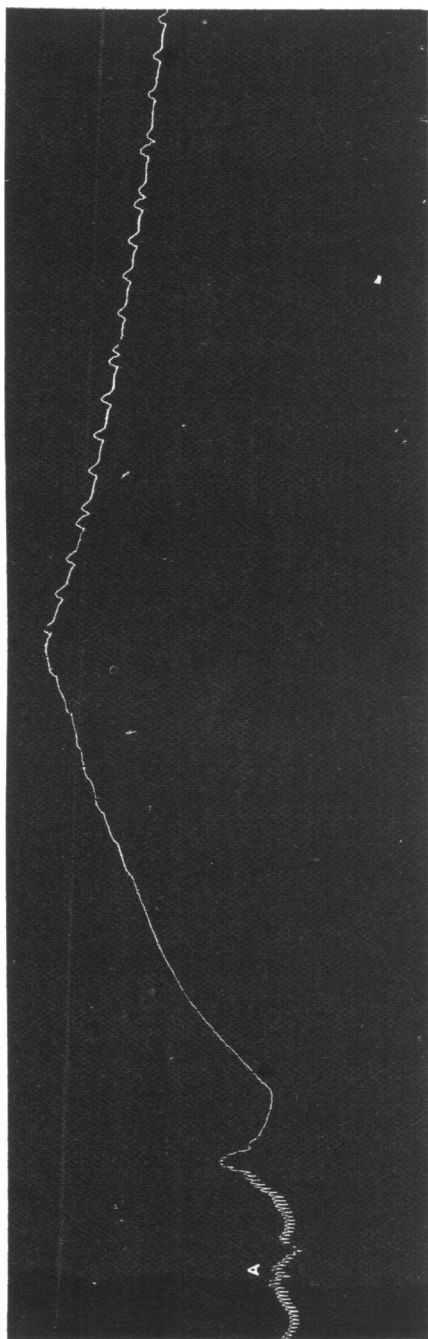
Fig. 26.  Effect of injection of rather larger dose of extract of human suprarenal.

## VIII. MODE OF DISPOSAL OF THE ACTIVE PRINCIPLE OF SUPRA-RENAL CAPSULE IN THE ORGANISM.

Our first experiments on this part of the subject were directed to ascertain whether the principle is eliminated by the kidneys. In order to determine this point we first injected a definite amount of suprarenal extract into the blood vessels of the dog, and obtained the usual marked physiological effect, lasting 4 minutes. We then clamped the renal blood vessels so as to eliminate the action of the kidney and injected a precisely similar amount. The duration and extent of the effect were, as far as we could determine, as nearly as possible exactly similar.

In a similar experiment we determined the effect of a definite amount of the extract before and after clamping the suprarenal capsules. This operation also produced, in our experiment, no appreciable effect upon the extent and duration of the action of the principle. It then occurred to us that the material might in some way become destroyed by direct action of the alkaline salts of the plasma or of some other principle in the blood. We accordingly mixed a certain amount of supra-renal extract with arterial blood from a dog, and a similar amount with a normal saline solution. The two portions of extract were then allowed to stand for 22 hours, the one in contact with blood, and the other with salt solution only. On injection of the same amount of these two fluids we obtained almost precisely similar results. We conclude therefore that the blood itself has little or no tendency to destroy the active principle.

The action upon the muscles appears to be prolonged beyond that upon the heart and blood vessels (p. 263); and we have concluded from this that it is possible that the active principle may be for a time at least stored away within the skeletal muscles.

## IX. CONCLUSIONS.

It appears to be established as the result of these investigations that, like the thyroid gland, the suprarenal capsules are to be regarded although ductless, as strictly secreting glands. The material which they form and which is found, at least in its fully active condition, only in the medulla of the gland, produces striking physiological effects upon the muscular tissue generally, and especially upon that of the heart and arteries. Its action is to increase the tone of all muscular tissue, and this result is produced mainly if not entirely by direct action. On the other hand the removal of the suprarenal capsules produces extreme

weakness of the heart and muscular system generally, and great want of tone in the vascular system. A similar result is known to be characteristic of advanced disease of these organs (Addison's disease). It may fairly be concluded therefore that one of the main functions, if not the main function, of the suprarenal capsules is to produce a material which is added in some way or another to the blood, and the effect of which is to assist by its direct action upon the various kinds of muscular tissue in maintaining that amount of tonic contraction which appears to be essential to the physiological activity of the tissue. Any further conclusion than this we cannot legitimately draw from our experiments, and we do not propose at this time to discuss such other conclusions as it may be possible to arrive at from the results of ablation experiments[1].

## ADDENDUM.

Since writing the above we have seen in the *Centralblatt f. Physiologie* (No. 4, Bd. ix.) an account of experiments by Szymonowicz and Cybulski upon the effect of intravenous injection of extracts of suprarenal capsules, and Prof. Cybulski has been good enough at our request to send us a copy of the original papers, which are apparently preliminary in nature[2]. These communications are nearly a year later in date than our first preliminary communication to the Physiological Society[3], but the observations have been made apparently without knowledge of our work. It is satisfactory to find that certain of our facts and observations have been thus independently confirmed; at the same time we cannot avoid noticing certain striking divergencies. We have kept back this present communication for a month that we might take the opportunity of repeating some of our earlier work in order to determine whether we had made mistakes upon the points of divergence. We have however not seen reason to alter any of our original statements.

The main point of difference is that according to Szymonowicz and Cybulski the extract acts not directly upon the blood vessels but upon the vasomotor centre. In confirmation of this they state that the

[1] We are indebted to Messrs Willows, Francis and Butler for furnishing us with a large supply of suprarenal material for the purposes of our experiments, and to Mr B. Moore for assistance in the many and complicated manipulations necessitated by the simultaneous registration of the volume or pressure-curves of the organs investigated.

[2] "Ueber die Function der Nebenniere," *Vorgelegt in d. Sitz. der Akad. d. Wissensch. in Krakau* vom 4. Febr. u. 4. März, 1895.

[3] *Proc. of the Physiol. Soc.*, March 10, 1894, in this *Journal*, Vol. xvi.

action is not obtained after section of the cord. We have however found that the activity is just as great after section of the cord and even after section of the nerves to a limb, and, in the frog, after complete destruction of the central nervous system; we are unable therefore to understand how it is that the Polish physiologists have arrived at a different conclusion. The chief points in which they confirm our observations are in the fact that boiling does not destroy the extract (although we find that prolonged boiling does so); that the medulla is more active than the cortex (we find the cortex inactive); that the cardio-inhibitory centre is stimulated by the extract; that the active principle is destroyed by alkalies, but not by acids, nor by gastric juice; that the active principle dialyses; that it is active in very minute doses; that the effect on the respirations is but slight. On the other hand, Cybulski finds that drying (at 110° C.) destroys the action, whereas we have usually employed dried material to obtain our results; that alcohol dissolves the active principle (which we find not to be the case for absolute alcohol); that while arterial blood does not destroy the active principle, permanganate of potash does[1]. On this fact Cybulski founds a theory that it is got rid of in the body by oxidation. The most important facts added by Cybulski are contained in the statements that the blood of the suprarenal vein contains the active principle of the gland in sufficient amount to produce marked physiological symptoms, and that the changes in the circulatory and respiratory systems accompanying deprivation of oxygen are no longer obtained in animals which have been deprived a few hours previously of their suprarenal capsules. These statements we have not as yet had the opportunity of testing[2].

*June* 24, 1895.

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2. Foà and Pellacani. Ibid. VII. 1884.
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4. Mattei, Eug. di. Arch. per le sci. med. VI. 1883.
5. Marino-Zucco, F. Chem. Centralblatt, 1888.

[1] Moore has found that oxidation of an active extract with $H_2O_2$ materially weakens the physiological effects. (*Proc. Physiol. Soc.*, March, 1895.)

[2] Note added on July 9th. I have now carefully tested these statements in three cases but have been unable to arrive at the same results. They are undoubtedly incorrect. The absence of asphyxial symptoms observed by Cybulski was probably the result of severe shock. (E. A. S.)

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18. Moore, B. Proc. Physiol. Soc., March 16, 1895 (This Journal, xviii., p. xiv).