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T H E R E L A T I O N B E T W E E N
N E R V E A N D I N T E R N A L
S E C R E T I O N .

By

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A. SUPRARENAL MEDULLA.

Part I.

RELATION OF NERVE TO GLAND.

1. Centre for Adrenalin Secretion.

The amount of adrenalin poured out by the suprarenal glands in an animal is considerable. In the cat this has been found to be .001 m.g. per kilo. per minute. This constant secretion is controlled by the nervous system through a reflex path and by means of an "adrenalin centre". The centre was first investigated by Elliot⁽¹⁾ in 1912: this writer ascertained the quantity of adrenalin in the suprarenal capsules of the cat under various conditions.

In the course of his work he found that the suprarenals of pithed cats had a smaller adrenalin content than normal cats of the same body weight. Since the pithing was carried out by section of the crus cerebri Elliot concluded that the centre controlling the loss of adrenalin was close to the bulbar vaso-motor centre. In 1917 Stewart and

Rogoff⁽²⁾ reinvestigated the question. They ascertained the output of adrenalin by determining the quantity present in the suprarenal vein, using a strip of plain muscle as an indicator, and controlling their results by eye reactions: their experiments were on cats. They found that destruction of the cord between the 3rd and 7th cervical does not interfere with adrenalin output, whereas injury to the cord between the 4th and 6th thoracic prevents liberation taking place. In a further communication⁽³⁾ continuing the investigation by the same methods they find that the centre controlling adrenalin secretion lies between Th.I. - Th.VI. and probably is situated in Th.III. and Th.IV. It may be noted that there is a fallacy in their method of ascertaining the quantity of adrenalin liberated. Stewart and Rogoff have shown that the adrenalin in blood is contained entirely in the serum; they accordingly tested the effect of the serum on a muscular strip. In so doing they did not take into account the action which normal serum has on plain muscle. Their results cannot therefore be accepted as having such accuracy as they attribute to them.

Cannon⁽⁴⁾, four years later, repeated the work of these writers but came to a different conclusion.

He found that removal of the brain down to the level of the corpus quadrigeminus leaves the centre intact, while section below this level interferes with the output. He locates the centre near the upper edge of the fourth ventricle, thus agreeing with Elliot. The recent researches of Van Loeven⁽⁵⁾ confirm the results of Cannon, although Van Loeven does not refer to the point. He worked with decapitate cats and found that the decapitation produced definite lessening of the blood pressure response to adrenalin secretion; this result was obtained both in the cat and in the rabbit. On the whole, therefore, observations point to the centre being located in the mid-brain.

2. Splanchnic Nerves and Adrenalin Secretion.

Accepting Dogiel's account of the anatomical connection of the splanchnic nerves with the medullary cells and also the observation first made by Cybulski in 1896, that adrenalin appears in the blood of the suprarenal veins, several workers have sought to give a clear proof that the splanchnics control the secretion of adrenalin. Biedl⁽⁶⁾

failed to find increased secretion of adrenalin after stimulation of the splanchnics. Tscheboksaroff⁽⁷⁾ found that after stimulating the splanchnic on one side, a more potent extract was obtained from the gland of that side. Asher⁽⁸⁾ obtained similar results. Elliot⁽¹⁾, estimating the amounts of adrenalin in the glands of the cat by means of observing the rise of blood-pressure produced by injection into other pithed cats, concluded that faradisation of the splanchnics discharges adrenalin into the blood. This result was confirmed by Stewart, Rogoff and Gibson⁽⁹⁾; they found, in cats, that if the splanchnic nerves are stimulated, the suprarenals secrete, since the sensitized pupil dilates. That this result is due to liberation of adrenalin is shown by the fact that no change occurs in the pupil if the vena cava be occluded or if the heart be stopped. Section of the splanchnic nerves in the thorax leads to the disappearance of adrenalin from the blood of the suprarenal vein, but this result does not invariably follow if the splanchnics are cut in the abdomen. This effect is not merely an immediate one, for no adrenalin is poured out by the glands even weeks later. These writers also showed, in the same series of experiments, that the latent period

for adrenalin is very short, being about thirty seconds, but varying considerably. Gley and Quinquaud⁽¹⁰⁾ draw attention to the fact that these results are very difficult to obtain in the dog, stimulation of the splanchnics having no effect on the output of adrenalin. The difference is an anatomical one; in the dog, it is impossible, except by special technique, to expose the suprarenal and its vein without disturbing the splanchnics, but by employing this special method they obtain results similar to those obtained in cat and rabbit. In 1922, Tournade and Chabrol⁽¹¹⁾ showed that double adrenalectomy caused a progressive fall of blood pressure and that the pressure can be restored by transfusion of blood from the suprarenal vein of another dog. If the splanchnics are cut in the second dog, a fall of blood pressure is noted, and a rise on stimulating their peripheral end. Hence he concludes that the normal tonus of the splanchnics is adequate to keep up a constant secretion of adrenalin. All these experiments show clearly that stimulation of the splanchnics results in increased output of adrenalin. One explanation for this is put forward by Popielski⁽¹²⁾ who states that the splanchnics have a vaso dilator effect on the vessels of the

suprarenal medulla; thus their stimulation causes an increased blood-flow to the gland, thus flushing adrenalin into the venous blood.

It has been found by Elliot⁽¹⁾, that electrical stimulation of the splanchnics, even if prolonged, does not exhaust the store of adrenalin in the gland as much as stimuli proceeding from higher centres. Accordingly it has been suggested that the splanchnics contain fibres which produce anabolism in the gland. Opposed to this last view is the following consideration:- days after section of the splanchnics on one side, no difference can be found in the adrenalin content, anabolism seems therefore to proceed without central control. This question of anabolic influence is still undecided.

3. Higher Centres and Adrenalin Secretion.

The output of adrenalin has been shown to be increased by certain emotions, particularly by fear. The experiments on this subject fall into two main classes; in the first, the effect on the gland is estimated directly (Elliot, Stewart and Rogoff), while in the second, glycosuria is taken as a

measure of the adrenalin output (Cannon).

Elliot^(), in 1912, conducted experiments on cats, inducing fright by means of morphia, the administration of which produces particular terror in these animals. Estimating the quantity of adrenalin in the glands after the emotion, he found that the adrenalin content was exceedingly small, much smaller than could be produced by continued stimulation of the splanchnics. He concluded that fright caused an increased output of adrenalin. This is usually considered in accordance with the fact that emotions such as fear or anger are accompanied by symptoms suggesting a widespread autonomic excitation. The results of Elliot are directly contradicted by Stewart and Rogoff⁽¹³⁾ who estimated not the content of the suprarenals but the adrenalin output. Fright was produced in cats by a better method than the injection of morphia, namely, by confronting the cat with a barking dog. They found that fright was not accompanied by an increased output of adrenalin. This result is corroborated by Kieley⁽¹⁴⁾, using the fact that an individual who has received a dose of apocodeine is greatly disturbed at the threat of a second dose. This worker investigated two such cases in man. He obtained no indication of an

increased adrenalin output. It is to be noted that the experiments were few, that he had no adequate means of estimating the condition of the suprarenal function, and that the drug used, apocodeine, since it paralyses the sympathetic, invalidates the conclusions drawn.

Cannon⁽¹⁵⁾ in 1912 used the second of the two methods mentioned above: he relied upon the production of glycosuria. He found that fright in animals was accompanied by the appearance of sugar in the urine. This is in confirmation of Elliot's work, and further it is now generally accepted as a well known fact that in man emotional response to an emergency produces an increase in blood sugar and an accompanying glycosuria. In acute mania and other forms of insanity characterised by periods of intense excitement, temporary glycosuria is common.

That these results indicate that fright has an effect on the secretion of the suprarenals is very probable. According to Meyer and Frouin, diabetic puncture and stimulation of the cerebral cortex do not produce glycosuria after extirpation of the suprarenals, and according to Zuelzer the real stimulus to the genesis of glycosuria is adrenal secretion. Kahn⁽¹⁶⁾ found that emotion produced no

glycosuria after removal of the suprarenals. On the other hand it must be observed that many authorities (Eppinger, Falta, and Rudinger) consider that the glycosuria is due to an action of the autonomic nervous system directly affecting the pancreas, vagus fibres being supposed to have an inhibitory effect on the islands of Langerhaus. A possible explanation is furnished by the experiments of Brown⁽¹⁷⁾ (to be referred to later); by perfusion experiments on the cerebral vessels he concluded that adrenalin stimulates the vagus centre, so that this direct effect of parasympathetic fibres to the pancreas may be considered to indicate an increased suprarenal activity.

However, a certain amount of doubt must attach itself to results obtained by any other than direct methods. The least fallacious of the experiments on the relation between emotional states and suprarenal activity - those of Stewart and Rogoff - give negative results.

4. Relation of Sensory Nerves to Adrenalin Secretion.

The effect of stimulation of sensory nerves on the activity of the suprarenals was investigated by Elliot, who definitely concluded that such stimulation resulted in an increased output of adrenalin. Stewart and Rogoff⁽¹⁸⁾ obtained a different result. They claim that stimulation of a sensory nerve has no such effect. The most conclusive work on the subject is that of Cannon^(19,20), making use of denervated heart preparations (cats). He found that the increased heart rate in such preparations when a sensory nerve was stimulated was due to the output of adrenalin: such increase did not occur on clamping the suprarenal veins and repeating the stimulation. He criticises Stewart and Rogoff's results, pointing out that in their experiments the splanchnic nerves were being continuously stimulated by exposure.

Part II.

RELATION OF INTERNAL SECRETION TO NERVE.

I. To Autonomic Nerves.

(1) The effect of Adrenalin on the Nerves supplying Blood-vessels.

In 1894 Oliver and Schafer⁽²¹⁾ discovered that the extract of the medulla - though not of the cortex - of the suprarenal bodies injected intravenously produced a rise in blood-pressure due to a peripheral action causing increased tone of the musculature of the vessels and the heart: their experiments were performed upon dogs, cats, rabbits, guinea-pigs, and a monkey, and also upon frogs. These results were confirmed by Cybulski, who, however, considered that the vasoconstrictor effect was due to an action on the medulla: this is incorrect, for the frogs used by Schafer and Oliver in their original experiments were pithed, while similar results in mammals are now a matter of accepted fact: no investigator has confirmed Cybulski's conclusion.

As pointed out by Oliver and Schafer, the extract does not act equally on all arteries, and it

acts chiefly on those of the splanchnic area. It has a strong action on all the arteries of the skin and all medium sized arteries in the body, such as those of the salivary glands and the bucco-facial region; the brain vessels and the coronaries are not constricted; indeed, in most species, the coronaries are actively dilated. It has been shown by Collip⁽²²⁾ that the constrictor effect is not necessarily equal even in the two limbs of the same animal. Schafer and Oliver⁽²³⁾ observed this in some cases.

The fact that adrenalin contracts the smooth muscle of certain blood vessels and relaxes others of apparently identical structure and which respond similarly to electrical stimulation, suggests that it does not act on the contractile muscle substance proper. The marked correspondence with the response to sympathetic nerve stimulation implies that it acts on the nervous mechanism, and that the nervous mechanism is the sympathetic system, since it is only effective on tissues in relation to which sympathetic nerve fibres have developed. But as the response persists after nerve degeneration, and is even augmented, it is necessary to assume the

existence of some intermediate mechanism, related to sympathetic innervation, but not trophically dependent on it. Langley postulates a receptive substance developed at the myoneural junction. Schafer observes that this increases either in amount or sensitivity after degeneration of the sympathetic nerves supplying the tissue, as tissues so treated are sensitized to adrenalin.

Hartman⁽²⁵⁾, in investigating the cause of the fall in blood pressure when adrenalin is injected intravenously, found that there was a transference of the blood from the splanchnic area to the peripheral region. Hoskins, Gunning and Berry⁽²⁴⁾ by plethysmographic methods further showed that the vessels of the skin contract, while those of the muscles dilate. Hartman has found in relation to this differential action that adrenalin constricts vessels of the skin, mucous membrane and splanchnics and therefore drives blood into the muscles which are actively dilated for its reception through the effect on the ganglion mechanism. As the amount of liberated adrenalin rises, the peripheral effect overcomes the ganglion effect in skeletal muscle and in the intestinal vessels so that the

blood is reversed in its path. Although small doses cause a fall and large doses a rise, he considers that the above differential effect is the more important. It has been further shown that in laboratory animals commonly used this differential mechanism is absent in the rat and rabbit, present in the cat and dog, and that (25) in development the constrictor response appears first, the differential mechanism as far as concerns the active dilatation in skeletal muscles next appears, and later still, intestinal vaso-dilatation is possible as a result of adrenalin injections.

Further, under certain conditions the ordinary constrictor effect of adrenalin is replaced by a dilator effect. This is especially noticed whenever the sensitivity of the sympathetic innervation is lowered, as by prolonged exposure of the nerve (26) by long continued perfusion with adrenalin itself (27,28), by so-called autonomic drugs (29) and ions (30-32) that depress sympathetic or increase parasympathetic activity, and by degenerative nerve section (33,34).

Dale (35) has shown, for example, that ergotoxin abolishes the action of adrenalin on the con-

traction of the plain muscle of the vessels, and indeed it prevents the production of all those symptoms of sympathetic excitation which intravenous injection of adrenalin normally elicits: it does not prevent the inhibitory effects, and thus a reversal of the previous response to adrenal, for example, vaso-dilatation instead of vasoconstriction, may be obtained after injection of ergotoxin. Ergotoxin acts on the receptive substance, and thus it appears that the active vasodilatation obtained after its use is an action of adrenalin on dilator fibres the mechanism for which is not the myoneural substance; evidence is given later that it is a ganglion mechanism.

Very small doses of adrenalin cause a dilator action; for example, 1 c.c. of 1 in 100,000 adrenalin injected intravenously into a cat produces not a vaso-constriction but a dilatation. This was first established by Moore and Purington in 1900⁽³⁶⁾ and has since been investigated by Cannon and Lyman⁽³⁷⁾.

Various attempts have been made to explain the cause of this dilator action, and of these we may consider four:

- (a) That the effect is due to impurities in the adrenalin solution.
- (b) That the fall of pressure is due to a stimulation of a centre in the medulla.
- (c) That the fall is occasioned by stimulation of peripheral vaso-dilators.
- (d) That the adrenalin has a histamine-like action on the capillaries.

(a) Considering first the statement that the fall of pressure is due, not to adrenalin but to impurities, Pari finds that with freshly prepared extracts there is never a fall of blood pressure; dilute solutions which when fresh produced a constrictor effect were found to cause vaso-dilatation after being kept for some time. He considers the depressor substance to be choline. Hunt⁽³⁸⁾ is of the same opinion. Neither of these observers satisfactorily demonstrated that choline was present in their solutions, for there are no known means of conclusively demonstrating the presence of this

substance in such dilutions.

The view that pure adrenalin cannot cause a depressor effect has been abandoned since the substance has been isolated chemically and synthetized. A tracing is attached showing a marked fall of blood pressure (cat) produced by 1 c.c. of 1 in 1000.000 pure synthetic adrenalin chloride solution.

(b) Certain authorities consider that the depressor effect is produced by the stimulation of a centre in the medulla. Izquierdo⁽³⁹⁾ considers that small doses of adrenalin stimulate the depressor nerve, thus causing a fall of blood pressure. When larger doses are given, this fall is marked by the vaso-constrictor effect. Collip⁽²²⁾ notes that in cats lightly anaesthetised a fall of blood pressure is readily obtained with a small dose of adrenalin. This fall may be converted into a rise by deepening the narcosis: the depressor effect is particularly liable to occur when urethane is used as an anaesthetic. The theory that the depressor effect is due to an action on the medulla is untenable for two reasons: first, small doses of adrenalin may give a fall of blood pressure in decapitate animals; secondly, a fall may be met with after the depressors are cut, and the vagi. It need not therefore be

Cat. ♂. wt. 2600 gms. 14. Nov. 22. Ether.



Carotid Pressure.



Respiration.

25g

Signal Line.

Time.

↓ 1 c.c. 1 in 1,000,000 synthetic adrenalin chloride.

TRACING I.

discussed further.

(c) The most commonly held view is that the fall of blood pressure is due to stimulation of vasodilator nerve fibres to the vessels. Hartman and Fraser⁽⁴⁰⁾ studied this question firstly in relation to vasodilatation in the intestine; secondly, in relation to limb vasodilatation. As regards the mechanism for vasodilatation in the intestines, Gruber⁽⁴¹⁾ had previously shown that section of nerves to the gut prevents adrenalin vasodilatation. Hartman and Kilborn⁽⁴²⁾ showed that complete removal of the brain and cord did not affect it, and proved, by perfusing isolated loops of intestine, that section of the nerves between the ganglia and the periphery, or painting the ganglia with nicotine, or destruction of the ganglia, destroyed the depressor response. It thus appeared that the mechanism controlling intestinal vasodilatation, when adrenalin is injected into the general circulation, is located in the collateral sympathetic ganglia, probably in the superior mesenteric. As the result of similar work they found that the mechanism for the limbs is located both in the dorsal root ganglia and in the sympathetic ganglia. Thus the dilator effect of adrenalin appears to take place through the ganglia,

not, as in the case of vasoconstriction, through the myoneural substance.

(d) It has been put forward as a possible explanation of the depressor effect of adrenalin that the drug has an action of the capillaries similar to that of histamine, and that this effect is apparent in greater dilution than is the vasoconstrictor effect. The action of histamine on the capillaries is well known. The experiments in which dilatation has been shown to occur after ergotoxin would support this view as well as it supports the theory discussed immediately previously. It is, further, known that the administration of histamine reverses the vasoconstrictor effect of adrenalin. It is not, however, unique in this respect; for example, acid sodium phosphate produces a like reversal. Sodium carbonate, on the other hand, tends to convert the depressor effect into a pressor one (Collip²²).

As yet there is not sufficient conclusive evidence to justify a definite standpoint on this question.

The effect of adrenalin on the vasoconstrictor and vasodilator nerves in the systemic circulation having been considered, it may be further noted that adrenalin affects the vasoconstrictors of the

pulmonary vessels. This subject has received attention from several writers who give varying results. Brodie and Dixon⁽⁴³⁾ failed to find any constrictor effect from perfusion experiments: they obtained on the other hand a slight dilatation. Plumier⁽⁴⁴⁾ always obtained constriction and never dilatation, as also did Wiggers⁽⁴⁵⁾. Argyle Campbell⁽⁴⁶⁾ obtained similar results. Brodie and Dixon's dilator effects are ascribed by Tribe⁽⁴⁷⁾ to the chloretone which their solutions contained; this is doubtful. Schafer and Lim⁽⁴⁸⁾ repeated perfusion experiments and also performed experiments in the living animal. The pulmonary and systemic pressures being recorded simultaneously, they found that adrenalin definitely affected pulmonary vasoconstrictors. The animals used were cats, dogs, and rabbits.

(2) The effect of Adrenalin on Nerves supplying the Intestine.

All observers agree that adrenalin inhibits the movements of plain muscle. This it may do in a dilution as great as 1 in 10,000,000. Magnus

considered that nerves were necessary for this action; on the other hand the effect persists even after all nerves have degenerated: such degeneration of course does not necessarily affect the receptor substance of the myoneural junction upon which adrenalin acts in its inhibition of intestine, the effect produced being similar to stimulation of the sympathetic supply to the gut and thus being merely an example of the general action of adrenalin on the sympathetic.

Occasionally adrenalin has an excitatory action upon the plain muscle of the intestine; the same sample of adrenalin yet producing vasoconstriction if injected into an animal. The reason for this is unknown; theorising, however, it may be that when adrenalin causes an increased contraction of intestinal muscle, it stimulates via the ganglia of the para sympathetic which are found in the intestinal wall, just as a dilator effect may be produced in blood vessels by stimulation of the ganglia of the vasodilators. In this case an excitatory effect would not be observed after the sample of plain muscle had been treated by nicotine.

(3) EFFECT OF ADRENALIN ON THE PUPIL.

One of the most interesting mechanisms on which the sympathetic system acts is the pupillary response.

In the course of a series of experiments on cervical sympathetic section in which one or both cervical sympathetic nerves were cut or double resection of the superior cervical ganglia performed, opportunity was taken to study the effect of intravenous and subcutaneous injection of adrenalin on the eye. The animals used included cats, rabbits, one dog, guinea pigs and rats; the dog is not so suitable as the cat because of the close anatomical connection between vagus and sympathetic, while in the other animals the eye and ear effects of section were found to be variable and more transient. Later investigations on the effect of adrenalin were therefore confined to cats.

As is well known, stimulation of the cervical sympathetic in the normal animal causes dilatation of the pupil, retraction of the membrana nictitans, widening of the palpebral aperture, and protrusion of the bulb. The last is only occasionally well-

marked; and is best seen in rats and rabbits.

Lewandowsky⁽⁴⁹⁾ discovered that intravenous injection of adrenalin causes a transient dilatation of the pupil, while a subcutaneous injection is without effect. This was confirmed by Boruttan⁽⁵⁰⁾ and Langley.⁽⁵¹⁾

Subcutaneous injection, and instillation into the eye, produce a positive dilatation, however, when the superior cervical ganglion has been completely removed, at least forty-eight hours previously: further, the dilatation is maximal and prolonged over several hours. This was first shown by Meltzer and Auer⁽⁵²⁾ who considered that normally the superior cervical ganglion sends impulses to inhibit the dilator fibres of the eye and to stimulate the constrictor fibres - the reverse effect of stimulating the sympathetic trunk or injecting adrenalin. In this way they explain the increased response to adrenalin when the ganglion is removed.

An anomaly directly related to the question of adrenalin influence on nerve was noticed, and has several times been confirmed: adrenalin in great dilution was found to cause contraction of the pupil instead of dilatation: this only occurred if the eye had been sensitised by removal of the ganglion, -

not as the result of section only, nor in the normal eye. Protocols showing this are attached:-

I. Cat, male, white, 2800 grammes:

First operation on April 22, 1921, under chloroform. Right cervical sympathetic ganglion completely removed. On recovery from anaesthetic -

Right pupil strongly contracted, aperture lessened, and membrana nictitans one third across eye.

Second operation, May 3, 1921. Ether anaesthesia. Injections of adrenalin into R. jugular.

Results:-

<u>Adrenalin</u>	<u>R. Pupil</u>	<u>L. Pupil</u>
1 cc. of 1 in 400,000	Dilatation, immediate	Transient do.
1 cc. of 1 in 1,000,000	do.	do.
1 cc. of 1 in 2,000,000	do. slower	do.
1 cc. of 1 in 5,000,000	Negative	Negative
1 cc. of 1 in 6,000,000	Contraction	Negative

II. Cat, grey, male, 3500 grammes.

First operation, March 17, 1921. R. ganglion removed under chloroform. On recovery -

R. pupil contracted, membrana nictitans half across eye, aperture less, and eye somewhat receded.

Second operation, March 26, 1921, under ether.
Adrenalin injections into L. jugular. Results:-

<u>Adrenalin</u>	<u>R. Pupil</u>	<u>L. Pupil</u>
.5 cc., 1 in 1,000	Huge Dilatation	Transient do.
1 cc. of 1 in 200,000	do.	Negative
1 cc. of 1 in 1,000,000	Dilatation	Negative
1 cc. of 1 in 2,000,000	do.	Negative
1 cc. of 1 in 5,000,000	Contraction	Negative

2. The effect of Adrenalin on Skeletal Nerves.

There is evidence that adrenalin affects the myoneural junction in a nerve-muscle preparation. Oliver and Schafer⁽²³⁾ discovered that extracts of the suprarenal gland prolonged the curve of contraction obtained from skeletal muscle, the latent period being unaltered. In the frog they injected it into the dorsal lymph sac, in the mammal, intravenously; they considered the effect to be on the nerve. This Borrutau⁽⁵⁴⁾ showed to be correct, since the phenomenon does not occur with curarised muscle. Jokyo⁽⁵⁵⁾ was unable to observe a paralytic action on muscle, but he observed an increase of irritability of the nerve. Takayasu⁽⁵⁶⁾ confirmed these observations; adrenalin solutions of greater concentration than 1 in 1,000,000 having the effect of decreasing the contractions of frog muscle. Guglielmetti⁽⁵⁷⁾ states that adrenalin has no effect on unfatigued muscle, but that the effect on fatigued muscle is such as Schafer and Oliver describe. Since the effect is removed by section and subsequent degeneration of nerves, or by curare, the seat of action appears to be the myoneural junction.

Gruber and Fellows⁽⁵⁸⁾, on the other hand, state that adrenalin increases the height of

muscular contractions and decreases the threshold stimulus: it may be noted that they used cat muscle, whereas most of the other observations have been on frogs.

The most recent work on the subject is that of Yoshimoto, who investigated the action of adrenalin among other autacoids on motor nerve and on muscle. His conclusion is that the conductivity of nerve is not changed by this substance, and that the contractions of voluntary muscle are slightly lessened. Yoshimoto observes, however, that the concentration which causes this effect is far greater than any which occurs in the body; it may be taken that adrenalin has no effect on the motor nerves or on voluntary muscle in man.

3. THE RELATION OF ADRENALIN TO THE
PIGMENTARY SYSTEM.

Lieben in 1906 found that adrenalin produced melanophore contraction in frogs; this has been confirmed by numerous observers. The debatable point is whether this action takes place through the nervous system or not.

Hogben and Winton⁽⁵⁹⁾ found that they were unable to affect the response of the dermal melanophores by stimulation of the sciatic nerves. They were also unable to alter the response of the melanophores to adrenalin by the administration of doses of nicotine sufficiently large to paralyse the sympathetic ganglia. They are inclined to believe that the evidence for a nervous control is inconclusive. Two fallacies may be noted in their argument. In stimulating the sciatic nerves and obtaining no melanophore response they merely prove that the mechanism is not contained in the sciatic; the possibility of perivascular sympathetic innervation is not eliminated. The experiment with nicotine is by their own showing fallacious, for nicotine itself

produces melanophore expansion. Apart from these considerations, the results obtained by these writers would lead one to consider that a nervous control is very probable, for they find that the only reagents which induce melanophore contraction are those which excite sympathetic nerve endings, while those which bring about melanophore expansion are drugs such as apocodeine and nicotine which paralyse the sympathetic. It is interesting to note that the authors group ergotoxine with the sympathetic stimulants, considering the action different from that of apocodeine, whereas both these drugs are sympathetic depressants.

It is unsatisfactory to consider only results obtained in frogs. The clearest evidence is available that pigmentary response is related to the nervous system: one may especially cite the work of Sumner and Pouchet on fish, and of Brücke on the chameleon. These writers are agreed that the pigmentary response is part of a retinal reflex taking place through the nervous system.

We are here, therefore, dealing with a phenomenon in which nervous system and internal secretion are related. To what extent the one mediates the other in the normal physiological response of melano-

phones is not yet proven.

DESCRIPTION OF TRACINGS.

The attached tracings were obtained by a modification of the Cannon method for the denervated heart. They illustrate points referred to in the section on adrenalin, and were obtained by a method devised to study the blood pressure as well as the heart beat, in connection with the depressor nerve and its action on the heart after removal of the stellate ganglion (Walker). The essentials of the method were as follows:-

Under ether anaesthesia, the animal was injected with urethane an hour previous to the operation; the resulting anaesthesia was found adequate. The carotid artery was connected with a mercury manometer, while an intravenous tube was placed in the opposite jugular vein. Artificial respiration was maintained through a two way tracheal tube by an uninterrupted blast of warm air at the rate of 30 per minute. The mammary arteries were secured by a ligature including them passed behind the sternum from side to side in the 2nd intercostal space. The thorax was opened by cutting the 2nd, 3rd and 4th ribs on each side, and cutting across the sternum at the level of the fourth rib, the flap so formed being retracted anteriorly. The stellate ganglia were easily defined, and removed on each side. The thoracic wound was roughly repaired by stitches. The right

auricle and the right ventricle were attached to two threads working on the pulleys of the Schafer cardiomyograph, through windows formed by the two bared intercostal spaces. In this way the trauma of lungs due to exposure in long continued experiments was minimised, and, more important, the heart rate was not so liable to be affected by changes in temperature.

Tracing II. shows

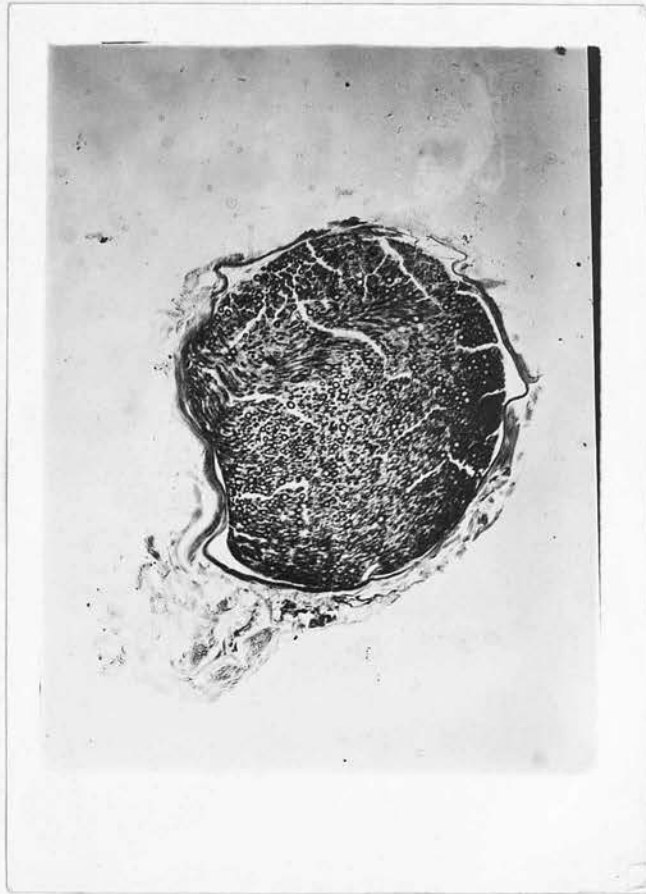
- (1) Typical depressor response to a moderately strong stimulus, 500 K.U., showing that separate depressors were defined in this cat. (Photographs of transverse sections of these nerves are attached.)
- (2) Effect on blood-pressure (fall from 68 mm. Hg. to 57 mm. Hg.) on removal of the stellate ganglia.
- (3) Effect of removal of the ganglia on the depressor response.
- (4) Result of stimulating the left sciatic nerve, before, during, and after clamping the suprarenal veins. The

suprarenals were exposed by a median abdominal incision, with the least possible exposure and handling of the viscera, and the veins clamped with small bull-dog clips.

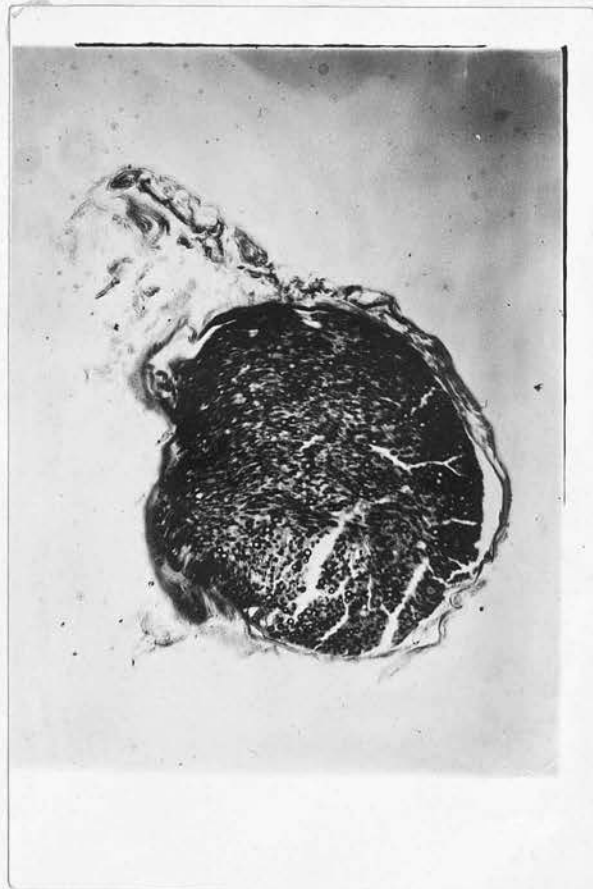
Tracing III.:

- (1) Left depressor and right depressor stimulated before and after an injection of 1 cc. of 1 in 50,000 adrenalin chloride diluted with mammalian Ringer's fluid.
- (2) Effect of removal of the stellate ganglia on blood pressure.
- (3) Depressor response before and after removal.
- (4) A second equal dose of adrenalin.

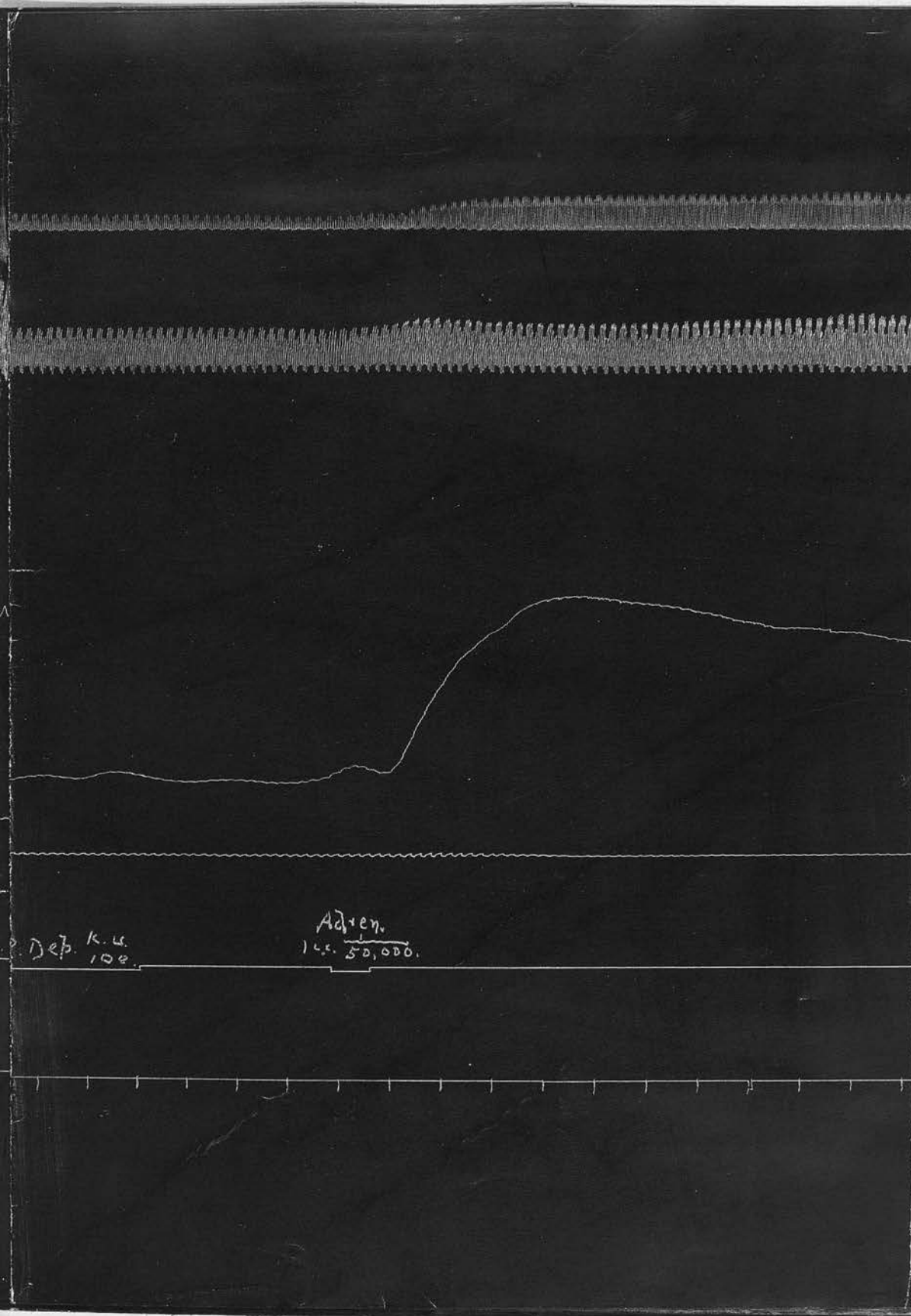
DEPRESSOR NERVES OF CAT
TESTED PHYSIOLOGICALLY.
SEE TRACING III.



LEFT DEPRESSOR NERVE X 120.



RIGHT DEPRESSOR NERVE. X 120.



TRACING II.

Rabbit ♂ 2250 kils
Edwin
Mathews 329
26.11.25.
R. Church

R. Ventricle

Cardial B.P. 70 mm Hg

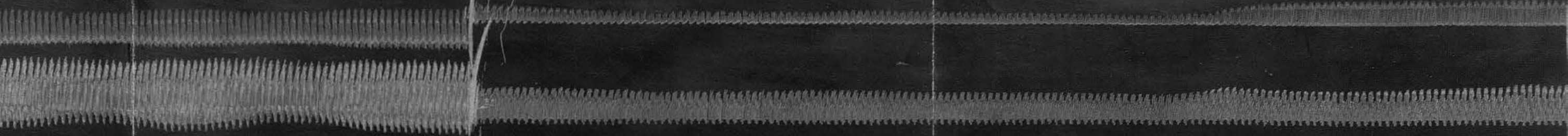
Resp.

Signal 6. Dep. 200 K.U. units
L. Dep. 100 K.U.
L. Vag. 100
R. Vag. 100 K.U.
R. small fibrot. E. Vagus 100 K.U.
R. Dep. 100.
L. Dep. K.U. 100
R. Dep. K.U. 100
A. Dep. 100 c.c. 50,000
L. Dep. K.U. 100.

Time 11:26 a.m. 11:28

TRACING II.

Stollates
Removed



22.2 mV

L. Dep. K.V. 100.

R. Dep. K.V. 100.

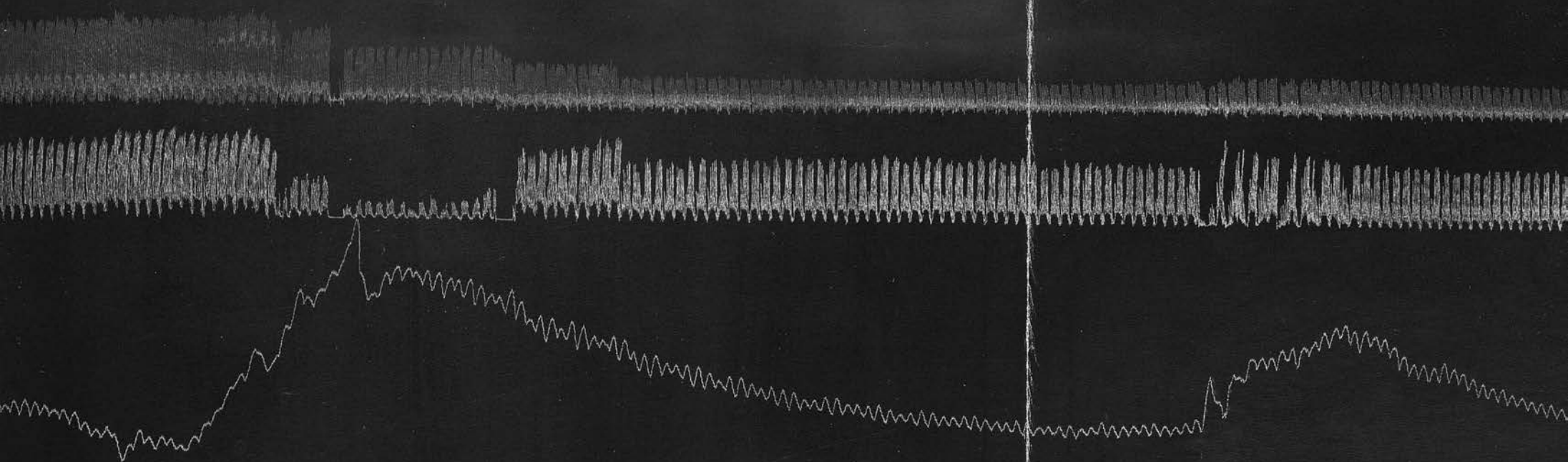
L. Dep. K.V. 100.

R. Dep. K.V. 100.

Adren.
14. 50,000.

Clot





Clamps Removed. from Suprachordal Pedicles.

L. R.

Stim. L. Sciatic - K. 500

12.52.

TRACING III.

B. SUPRARENAL CORTEX.

It is generally recognised that the cortex of the suprarenal is essential to life.

Tizzoni observed severe lesions in the central and peripheral nervous system after extirpation of the glands. He described extensive destruction of nerve fibres and ganglion cells in all parts of the nervous system. His work is not reliable, since removal of the gland included removal of the medulla, and secondly, since he recorded death after removal of one suprarenal, this being opposed to the experience of every subsequent investigator. Donetti⁽⁶⁰⁾ states that removal of the glands produces changes in the nerve cells of the central nervous system, the nuclei becoming vesicular and granulated. These changes occur especially in the medulla.

It has been suggested that there is a relation between the adrenal cortex and the highly developed brain in man. Alexander and Kohn⁽⁶¹⁾ have each put forward the view that the adrenal cortex produces lecithin, this being utilised in the development of the brain. This is pure speculation.

Meyers⁽⁶²⁾ suggests that the secretion of the cortex may neutralise toxins which act upon nerve. He supports this by a series of experiments in which he mixed cobra toxin and extracts of suprarenal cortex, and found that the toxin was rendered inert. This merely proves what no one would deny, that the cortex contains lipoids; it throws no light on the relation of the cortex to nerve.

Elliot observed that section of the splanchnic nerves produces no histological change in the cells of the suprarenal cortex.

It may be concluded from the foregoing that there is no evidence for any physiological relation between nerve and the suprarenal cortex.

C. PITUITARY.

RELATION OF NERVE TO PITUITARY AUTACOIDS.

There is comparatively little known regarding the relation between the nervous system and the pituitary body. The experiments of Jacobson, Cushing and Weed⁽⁶³⁾ demonstrate that one of the pituitary hormones is secreted in greater quantity when nerves passing to the gland are stimulated. These investigators stimulated the superior cervical ganglion, and observed that sugar appeared in the urine, whether the stimulation was faradic or mechanical; the animals used were dogs, cats and rabbits. They found that this result persisted after all possible paths for downward passage of impulses had been blocked, and that, if the pituitary body was removed before the stimulation, no such result was obtained. They accordingly concluded that the stimulation of the cervical sympathetic caused liberation of a pituitary hormone, and produced thereby glycosuria. Shannoff confirmed these experiments. Pighini⁽⁶⁴⁾ found that after vagus section, there was hyperfunction of the pituitary, a result in

accordance with the findings of Cushing and his co-workers.

Little is known of the action of the pituitary hormones on nerve. The best known, pituitrin, has no effect on the nerves of the autonomic system; drugs acting on sympathetic and parasympathetic nerves do not produce any alteration in its action.

Certain experiments of Toshio Uno are of interest in showing the effect of nervous excitement on the pituitary. Male albino rats, by repeated electrical stimuli, were kept constantly excited for three to six hours. The pituitary, thyroid, and suprarenal glands were then removed and examined. The only significant changes were found in the pituitary. In the rat, normally, pars glandularis causes a contraction of intestinal muscle, pars nervosa a relaxation; combined extracts have an intermediate effect⁽⁶⁵⁾. In these experiments the pituitary weights were greater than the controls, and the extract from them had a marked effect on plain muscle, whereas the extract from the controls had no effect. These results have not been confirmed.

It is well known that pituitary tumours and derangements are in general accompanied by mental

depression and dullness; this, however, cannot be considered as a direct action on the higher centres, but is more probably the result of a wide-spread disturbance involving other ductless glands.

D. GENERATIVE ORGANS.

RELATION OF NERVE TO THE AUTACOIDS OF THE GENERATIVE ORGANS.

There is a considerable mass of evidence that the autacoids of the testis and ovary influence the nervous system. The observations on this point may be regarded under two heads :- the effect of administering extracts of the glands; and the effects following removal, or disease, of the generative organs.

The well known experiments of Brown-Sequard, who found that the taking of extracts of testes was followed by a feeling of increased vitality and a diminution in the symptoms of age, have had much doubt cast upon them, since most recent observers have not met with similar results. Stanley⁽⁶⁶⁾, however, repeating his experiments, states that good results were obtained by the injection of testicular extract into convicts: these subjects became brighter mentally and improved physically. Stanley also reports great mental improvement obtained in this way in cases of paranoia.

The changes in disposition of animals which result from removal of the generative organs have not been definitely demonstrated to be a direct effect on the nervous system: that the action is indirect is improbable, since no symptoms which suggest disturbance of other ductless glands are seen. The experiments of Nussbaum suggest that the action is, in some respects at least, dependent upon nerves. Male frogs develop, at the breeding season, a swelling of the thumb, and hypertrophy of the muscles of the forearm: these changes are prevented by castration, but appear again on the ingrafting of a portion of testis, and are therefore clearly dependent on autacoids from the testis. Nussbaum found that section of the nerves of one limb prevented the development of the hypertrophy of the thumb and the muscles. He thus proved that the autacoid concerned in this case acts on the local tissues not directly but through the nervous system. Most of the occurrences related to the functions of the ovary and testis are admittedly not dependent on the nervous system, to whatever extent they may be affected by it. The researches of Goltz, who showed that pregnancy and parturition can occur in an animal without a lumbar cord, place

this beyond doubt.

Wheeler and Shipley⁽⁶⁷⁾ have shown that a relation exists between the autacoids of the testis and the sympathetic nervous system. Using as an indicator for the activity of the sympathetic system the vasomotor response to nicotine, they found that in castrated dogs the sympathetic system is depressed in activity: the normal activity is restored by a testicular graft. In females, on the other hand, removal of the ovaries is followed by an increased irritability.

That there is a sympathetic supply to the ovary and testis has been shown by Ranson. It is obviously not necessary for the production of the internal secretion of these glands, since functional grafts of ovary and testis maintain the secondary sexual characters as well as do the glands in situ. It is indeed stated that section of the sympathetic nerves to the testis causes a hypertrophy of the cells of Leydig, which are recognised to be responsible for the autacoid production in the male gonad. The experiments of Ribbert⁽⁶⁸⁾, Rubintein⁽⁶⁹⁾, Halban⁽⁷⁰⁾ and others, on ovarian grafts, confirm the original observations of Knauer⁽⁷¹⁾, who showed that grafts of testis in ovariectomised animals caused

atrophy of the uterus, whereas grafts of ovary prevented the atrophy, thus proving the efficacy of grafts, apart from nervous control.

The wide-spread chromatolysis met with in the central nervous system in dementia praecox, where the interstitial cells of the gonads are degenerated, are of importance in connection with this subject. The fact that this condition appears at puberty, and that it is accompanied, or preceded, by a degeneration in the testis and ovary, strongly suggests that there is a direct relation between these glands and the central nervous system. On the other hand, as Mott observes, both changes may be the result of a generalised disturbance, wherein there is a failure of oxidature processes⁽⁷²⁾.

E. PARATHYROIDS.

RELATION BETWEEN THE PARATHYROIDS AND NERVE.

The fact that removal of the parathyroids is followed by a train of symptoms suggestive of nervous disturbance was first established by Vassale and Generali, who removed the parathyroids from ten cats and nine dogs. Fibrillary twitchings, muscular spasms, inability to walk and depression, were among the symptoms observed. All the animals, except one, died within ten days. These sequelae were, as Vassale and Generali pointed out, those which, since thyroid-extirpation had been introduced by Schiff, had been noted as following thyroid removal. Later, the same workers showed that if one of the four parathyroids was left in situ, no symptoms appeared. Their results have been amply confirmed by several investigators, especially by Swale Vincent and Jolly.

The muscular twitchings apparently have their origin in the central nervous system, since section of motor nerves stops them; section and degeneration of the posterior roots has no effect, and

section of the cord does not remove the spasms in muscles posterior to the level of section; the efferent neurones in the cord are thus the structures affected⁽⁷³⁾. Peripheral nerves are also affected, for Paton and his co-workers have shown that the electrical excitability of the nerve muscle preparations from parathyroidectomised animals is increased.

It appears, therefore, that the effect of removal of the parathyroids is to cause an increase in the excitability of nerve; the nerves most affected are the motor nerves to muscle, although the irritability of the sympathetic nerves is also increased, as shown by Hoskins and Wheeler.

It is only necessary to consider briefly here the way in which this increased excitability is produced. McCallum considers that it is due to a deficiency of calcium salts; Sabbatini and others have shown these to be capable of diminishing the excitability of nervous tissues. Paton considers the fault to be in a disturbance of guanidin metabolism.

It is certain that the toxic agent is in the blood, for cross-circulation experiments prove that if the leg of a normal animal be supplied with the blood from an animal with tetany, hyperexcitability

soon shows itself in the normal limb. Paton has demonstrated that guanidin is increased in the blood of dogs with tetany from 1 mg. per litre to ten times that amount. He considers the injection of calcium salts, which check tetanic spasms according to McCallum, as acting merely as a sedative. It has never been satisfactorily demonstrated that there is an alteration in the calcium content of the blood in tetany; and the fact that bleeding an animal and replacing the lost blood by calcium free Ringer, relieves tetany as much as does the injection of Calcium, must be considered as an important argument against the theory of McCallum⁽⁷⁴⁾.

Working on frog nerve-muscle preparations, Yoshimoto⁽⁷⁵⁾ showed that blood from a parathyroidectomised animal increases the excitability of isolated nerve, but produces no twitching, and has no effect on muscular contraction, unless large doses are employed, when depression results. In this way it is similar to guanidin carbonate. Paton found serum from animals with tetany to act similarly to guanidin, in producing muscular tremors and twitchings. Experiments of this nature are, however, to be regarded with caution, for guanidin produces no effects in certain animals.⁽⁷⁶⁾ Among the results

of parathyroidectomy is one met with in severe cases of tetany, - epileptic fits, suggesting a stimulation not only of peripheral nerve but of the cerebral cortex. The experiments which show that the parathyroid secretion influences the cortex are those of Hammett⁽⁷⁷⁾. This observer removed the parathyroids in tame and untamed rats: he found the operation fatal in 79% of the cases where wild rats were employed, but only in 13% of the cases where the operation was carried out on tame ones. This remarkable result he attributes to a greater stability of the higher centres in the tame animals. It is, however, slender evidence from which to argue a direct action on the cerebral cortex.

F. THYROID.

RELATION OF NERVE TO GLAND.

Parameschko⁽⁷⁸⁾ first described, in 1867, nerves passing from the arteries of the thyroid gland towards the intervesicular connective tissue. His observations were amplified by several other histologists. Poincare⁽⁷⁹⁾ suggested that these nerves might have a secretory function, while Berkley⁽⁸⁰⁾, Andersson⁽⁸¹⁾ and Rhinehart⁽⁸²⁾ have added to the details of their course. Rhinehart states that nerves are derived from sympathetic ganglia, that they form perivascular plexuses, and, from those, perivesicular plexuses, the terminal fibrils ending in relation to the bases of secretory epithelial cells. According to him all nerves entering the thyroid gland are non-myelinated.

Briau⁽⁸³⁾, by anatomical and embryological methods, has traced the thyroid nerves from the cervical sympathetic trunk. They leave the trunk at different levels, in man principally from the middle cervical ganglion. They then form plexuses round the thyroid arteries, chiefly the inferior thyroid.

Poirier and Charpy describe similar branches from the superior cervical ganglion accompanying the superior thyroid artery. The existence of these nerves being admitted, demonstration of a secretory function is desirable. Cannon and Cattell⁽⁸⁴⁾ found that by stimulating the sympathetic high in the thorax, a current of action was evoked from the thyroid after a latent period of about five seconds. This current did not occur as a result of excitation of the vagus anterior to its union with the cervical sympathetic strand. Since the vagus contains motor fibres to the muscles of the larynx, curarized animals were used; further, the animals were decerebrate. These observers were quite unable to demonstrate that vagal stimulation produced any action current in the gland. As further evidence one may note that the injection of pilocarpine, which excites cranial autonomic fibres, has no effect on the current from the gland. In order to show that these results were not due to an anaemia of the gland following sympathetic stimulation, the carotids were clamped for a period equal to that during which stimulation was carried out: no electrical change resulted from this procedure.

From these experiments Cannon and Cattell con-

cluded that the non-myelinated fibres passing to the thyroid are derived from the sympathetic and not from the cranial division of the autonomic, and that they are true secretory nerves.

An excellent demonstration of the correctness of this conclusion would be to show that an anastomosis between the cervical sympathetic and a nerve constantly carrying impulses, such as the phrenic, results in signs of increased thyroid activity. Such an experiment was performed by Cannon and Fitz⁽⁸⁵⁾. They united the anterior root of the right phrenic with the right peripheral cervical sympathetic so that after regeneration impulses over the phrenic might pass to the superior cervical ganglion. They claimed that in four out of six cases symptoms of hyperthyroidism were obtained, tachycardia, increased basal metabolism, and, in one cat, exophthalmos, and that the condition was cured by removing the thyroid of the same side. Troell⁽⁸⁶⁾, Langley⁽⁸⁷⁾ and Burget⁽⁸⁸⁾ repeated this experiment without success. Wilson⁽⁸⁹⁾, in 1916, by experimental production of a bacterial lesion in the superior cervical ganglia in goats, found changes in the ganglia and in the thyroids similar to those met with in exophthalmic goitre: this would tend to

support the evidence for a nerve mechanism controlling thyroid secretion.

Kummer⁽⁹⁰⁾, however, showed that thyroid grafts will function adequately to the animal's needs whether implanted in the region of an autonomic nerve supply or not, so that nerve control is not essential.

It is, however, to be considered as proved by the investigations of Cannon and his co-workers that the thyroid secretion can be influenced by nerve stimulation. This is admitted by all observers, but many consider the secretory fibres to be derived from a cranial autonomic source. Foremost among these are Asher and his colleagues.

Asher and Flack⁽⁹¹⁾ followed Cyon's⁽⁹²⁾ suggestion that the laryngeal nerves are the secretory nerves to the thyroid: they stimulated these nerves in the rabbit and found that simultaneous stimulation of the depressor caused a greater fall of arterial pressure than occurred when the depressor alone was stimulated: further, they found that during excitation of the laryngeal nerves, the effect of adrenalin on blood pressure was greater than before. Since the same occurrences follow an intravenous injection of thyroid extract, they conclude

that the laryngeal nerves produce a true secretion. Biedl and Brun⁽⁹³⁾ confirmed the result, but since they note that uniform stimuli applied to the depressor gives a variable fall, they do not consider Asher's contention proven. Schafer⁽⁹⁴⁾ has been unable to confirm the results of Asher's experiments. Oswald, however, states that thyreoglobulin and other iodine compounds increase the sensitivity of the vagus and depressor; at the same time he notes that it increases the sensitivity of the sympathetic. Asher's experiments merely show that the laryngeal nerves contain fibres which influence the secretion; the question as to whether they are sympathetic or parasympathetic is undecided, since the laryngeal nerves may contain sympathetic fibres.

Cannon attempted to elucidate the matter further by making use of the denervated heart as his test tissue. In this preparation the stellate ganglia were removed by small lateral openings in the thorax and the vagi sectioned in the thorax under artificial respiration. The thoracic windows were then repaired and natural respiration re-established by a momentary continual blast. The response of the denervated heart under light ether anaesthesia is remarkably constant and is only affected by

chemical and thermal changes. He found that an increase of heart rate in the cat, amounting even to 25%, is caused by gentle massage of the thyroid: this rise of rate takes from half to one hour to develop, and results even if the suprarenals are excluded from the circulation. Control massage of the submaxillary is without effect. Stimulation of the cervical sympathetic has the same result and only if the thyroids are present. Stimulation of sensory nerves and asphyxia cause a brief acceleration due to adrenalin only if the thyroid has been removed: if not, there is primary acceleration due to adrenal secretion, followed by the slow development of the thyroid rise.

There are thus two distinct points of view regarding the secretory innervation of the thyroid. First, that of Cannon, who considers the nerves are sympathetic in origin. He admits that stimulation of the laryngeal nerves may cause similar effects, and says he has actually obtained acceleration of the denervated heart on excitation of the superior laryngeal. He argues that this result may be due to sympathetic fibres running in the laryngeal nerves. He might with reason add that the anatomical evidence of Rhinehart that nerves pass from the

sympathetic neighbouring ganglia, and are non-myelinated in their course, carries with it a strong probability that these nerves are sympathetic.

Asher, on the other hand, still considers the laryngeal nerves to be the nerves controlling the secretion, and believes the secretion to be under parasympathetic control.

As regards the secretory innervation of the thyroid, some light may be thrown on the difficulty by reconciling Asher's results with those of Cannon by considering one or two anatomical findings in the course of an investigation into the morphology of the depressor nerve: and also by consideration of the physiology of the depressor in relation to the thyroid.

1. Anatomical findings: In a large number of animals examined, including cats, rabbits, dogs, guinea-pigs, rats, and one horse, a strand was found to pass from the depressor (when present) to the

superior cervical ganglion. Cyon⁽⁹⁵⁾ described such a connection in the dog and in the horse, and called it the third root of the depressor. Further, in the cat, rabbit, dog, and horse, a definite plexus of fine sympathetic fibres was occasionally seen ramifying from the superior cervical ganglion round the origin of the superior laryngeal from the vagus, and along the superior laryngeal nerve beyond the point of origin of the laryngeal root of the depressor. This would tend to support the view of Cannon that any result indicative of thyroid secretion obtained by stimulation of the superior laryngeal nerve is due to sympathetic fibres which may be running with it.

Secondly, it is to be noted that in cats and rabbits a fairly constant connection was found between the sympathetic at the level of the inferior cervical ganglion and the depressor, either by a small plexus or by a branch joining the depressor from the inferior cervical ganglion.

This similarly explains any positive effect obtained by Asher on stimulating the inferior laryngeals, since fibres from the inferior cervical ganglion have been found to accompany them.

2. Physiology. Cyon⁽⁹⁵⁾ states that the depressor carries vaso-dilated fibres for the thyroid gland, running in the superior laryngeal. If this is accepted, Asher stimulated vaso dilators to the gland and therefore his results require reconsidering from the point of view of his conclusions. He stimulated the depressor in its course with a minimal stimulus, and repeated, during simultaneous excitation of the cut superior laryngeal nerve just medial to where the depressor root leaves it; this caused a greater fall of blood pressure. He found similar results with the inferior laryngeal in certain cases.

As we have seen above, he concluded that

- (1) The superior laryngeal and inferior laryngeal carry true secretory nerves to the thyroid.
- (2) A substance, poured out by the gland under their influence, sensitizes the depressor.

There is no definite evidence to disprove the second conclusion, and we may accept it provisionally.

As regards the first point, his results are

sufficiently explained by assuming an out-pouring
of secretion from the gland due to vaso-dilatation.

EFFECT OF CERVICAL SYMPATHETIC SECTION
ON THE THYROID.

Experiments were made to determine the effect, if any, produced in certain internally secreting glands, and on the salivary glands, as a result of section of the cervical sympathetic. The animals used were cats, rabbits, guinea pigs, rats, and one horse - in all, 25 cats, 20 rabbits, 20 guinea pigs and 3 rats. In general the procedure was to resect under ether or chloroform anaesthesia and with aseptic precautions about two centimetres of the cervical sympathetic on one side, or to resect the superior cervical ganglion on one side: in this group the glands of the unoperated side were considered as a control both for weight and histological appearance. It has been generally stated that in an animal the two thyroids are very similar as regards weight and histological appearances, but in a large number of normal animals the thyroids, suprarenals and pituitary were examined post-mortem and the weights found to vary considerably. However, this objection was met as far as is possible with individual variation, by the second group in

which the cervical sympathetics of both sides were cut or the ganglia resected, animals of the same sex and body weight being used as controls. In neither group was there any significant difference in thyroid weight, nor in pituitary weight. Many other factors may influence the suprarenal weights, but it is sufficient to note that the only animal in the whole series which showed a marked increase in size and weight of the thyroid on the operated side, the right, was a pregnant rabbit, which showed also enormous hypertrophy of the suprarenals, especially the right, and of the right ovary.

In the more recent experiments on cats, care was taken to note if the depressor was present as a separate nerve, and if so, it was not sectioned: Table II. gives results in cats from this group.

In one cat, the depressor, found to be present as a separate nerve and tested by stimulation, was purposely cut. The protocol is:

Cat, black, male, weight 2050 grammes. See photographs B.(1), B.(2).

Operation, 6th December, 1921, chloroform and ether. Right cervical sympathetic and right depressor cut, and one centimetre resected from both. Right eye and ear symptoms well marked before recovery from anaesthesia.

Killed, 13th March, 1922, ninety-seven days later. Right thyroid appears atrophied compared with left.

R. Thyroid .067 grm.

L. Thyroid .102 grm.

The difference here appears to be significant, but no conclusion can be drawn from one result, and this point remains to be tested for specially.

It will be noted, however, that in Table II., although the differences are not shown corrected for body weight, the difference between the two sides is less than in the normal group, and less than in the group taken at random from those animals where the depressor was probably cut with the sympathetic. III. (It is to be noted here that in cats examined for the presence or absence of a separate depressor, it was found separate on the left side in thirty-seven out of fifty cats, on the right side in eighteen, in the others it coursed with the sympathetic and was only definable near its origin in eighteen, and not definable at all in five.)

The point is of importance in that as depressor stimulation can cause vaso-dilatation of the gland vessels, section of vaso-dilator fibres would explain the atrophy noted in the one case of depressor

section above, and the closer correlation in weights between the cut side and the normal where the depressor was known to have been spared.

Against this it must be stated that even when the nerve was separate, there were anastomoses between it and the cervical sympathetic which would make it impossible to state definitely that the dilators had been spared. By cutting above the usual level of the inferior cervical ganglion the fairly constant anastomosis between it and the depressor is avoided, but in every case of a separate depressor examined, a well marked strand led to the superior cervical ganglion. The existence of this latter anastomosis was noted by Cyon in the dog and in the horse. Further, Cyon definitely states that vaso-dilator fibres course with the depressor to the thyroid either by way of the superior laryngeal or the various nerve plexuses which the depressor forms with the sympathetic and vagus.

There is then no significant difference in weights which might indicate any change in secretory activity. Cannon has stated that section of the cervical sympathetic causes atrophy of the thyroid. Missiroli⁽⁹⁶⁾ noted this also.

The histological findings are also negative: the glands were fixed

and stained in the usual manner and show no constant difference, either in staining properties of the colloid, appearance of the epithelial cells, or size of vesicles.

The thyroid on the side of section appeared in some cases to show a larger proportion of small vesicles with almost no lumen, a tissue looking at first sight like parathyroid. This, however, could generally be demonstrated in the normal side also.

The cats which had the superior cervical ganglia removed, and young cats which had both cervical sympathetics cut, were found to be very susceptible to cold and died in a variable period after the second operation under conditions which suggested distemper. Results of such sections are for the present not discussed. Photograph D., however, illustrates the degenerative changes met with in the thyroid gland in such a case of removal of superior cervical ganglia.

Meltzer⁽⁹⁷⁾ noted that in ninety per cent of cases of double resection of superior cervical ganglia in cats, death occurred in two days, with marked pulmonary symptoms. It remains to be proved whether the post-mortem findings are due as he thinks to an internal secretion of the ganglia or

to increased susceptibility after removal.

The results as regards weight and histological findings of thyroid, suprarenals and pituitary in the rabbit, guinea-pig, rat, and in the horse, were also negative.

No evidence has therefore been found in this enquiry that section of the sympathetic nerve supply to the thyroid causes any change in the secretory activity of the gland.

TABLE I.

Normal Cats, unoperated.

No.	Body Weight in grams.	Thyroid Weight		Duration of Section
		Left. grms.	Right grms.	
1	2950	0.122	0.107	47
2	3200	0.079	0.105	90
3	3050	0.215	0.220	310
4	2700	0.150	0.185	68
5	2380	0.097	0.110	20
6	3300	0.149	0.130	30

TABLE II.

Right Cervical Sympathetic cut.
Depressor Nerve not cut.

No.	Body Weight in grams.	Thyroid Weight		Duration of Section
		Left grms.	Right grms.	
1	2150	0.112	0.109	30
2	2600	0.165	0.143	45
3	2550	0.107	0.098	18
4	3250	0.171	0.157	53
5	2050	0.103	0.117	27
6	2570	0.235	0.243	60

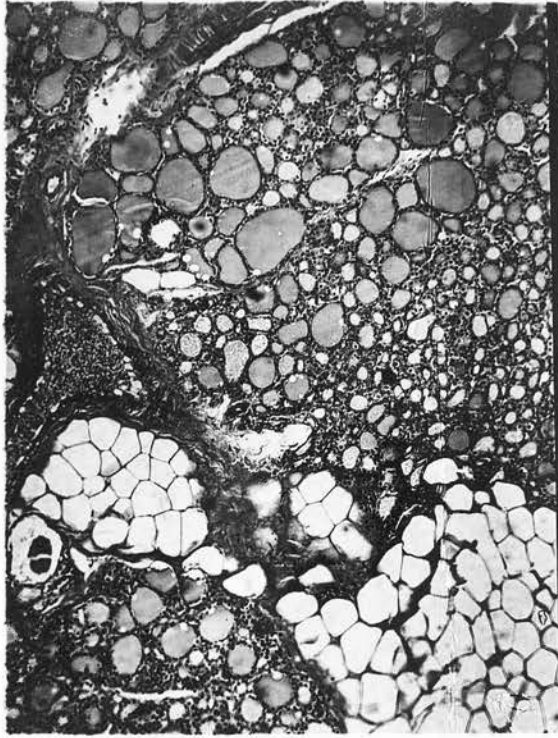
TABLE III.

Right Cervical Sympathetic section.
Depressor not noted.

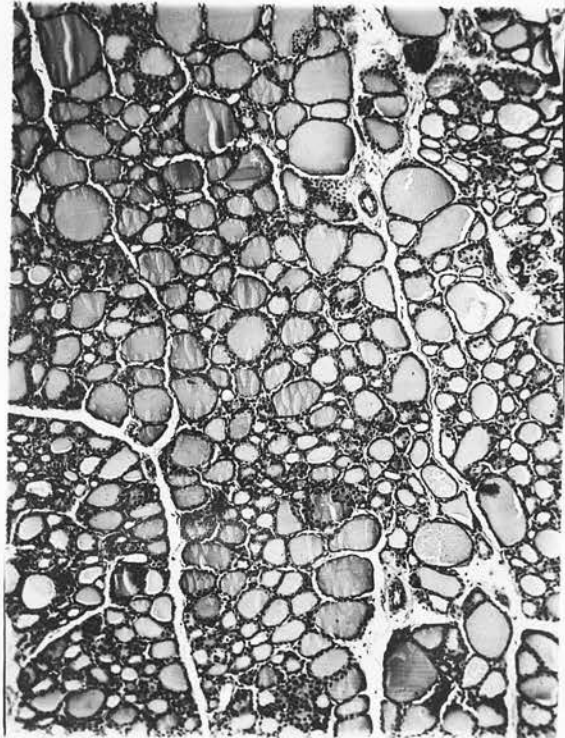
No.	Body Weight in grams.	Thyroid Weight		Duration of Section
		Left grms.	Right grms.	
1	2750	0.195	0.160	39
2	2500	0.210	0.159	47
3	3100	0.290	0.235	80
4	2900	0.125	0.104	51
5	2600	0.180	0.155	68
6	3250	0.091	0.121	30

RABBIT.

A.
RIGHT CERVICAL SECTION



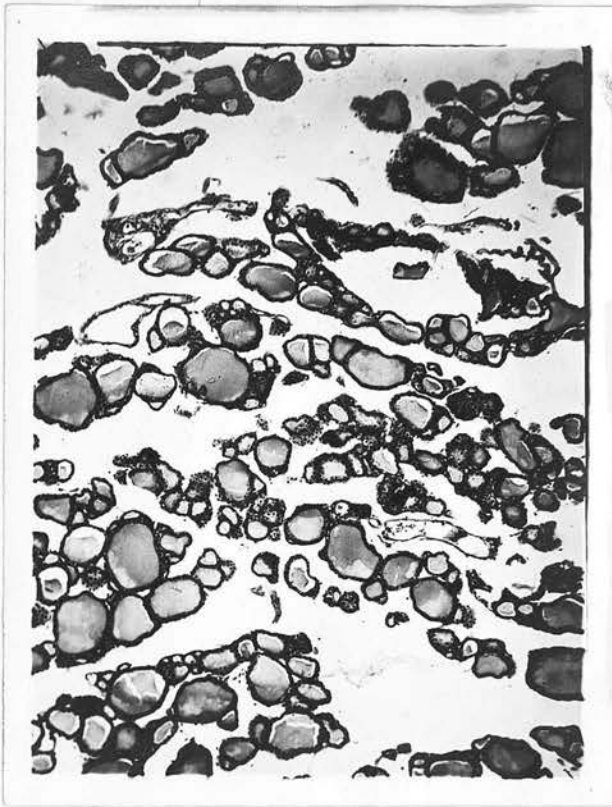
LEFT THYROID. X 90



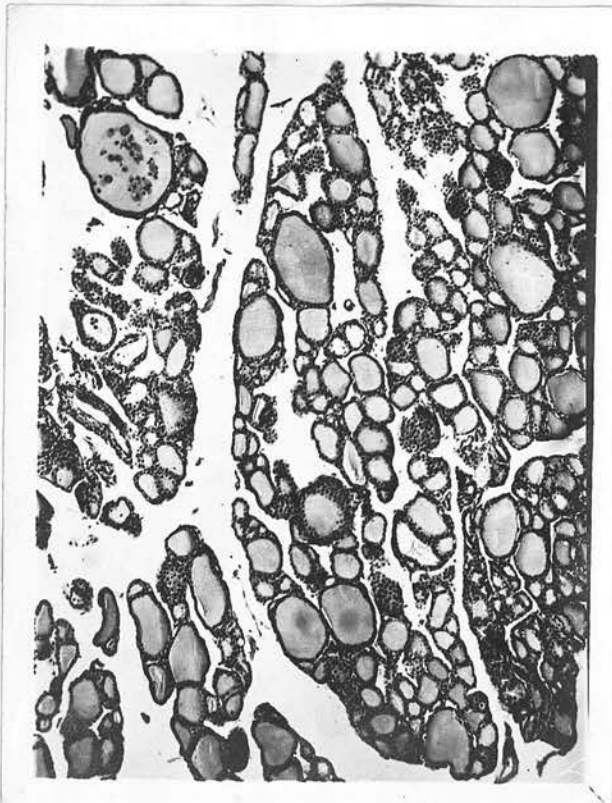
RIGHT THYROID. X 90.

B.

Cat. Right Cervical Sympathetic Section.



LEFT THYROID. X 90

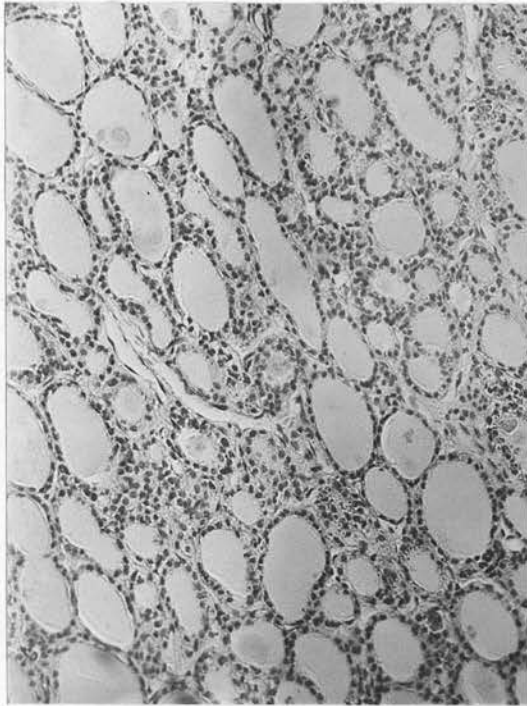


RIGHT THYROID. X 90

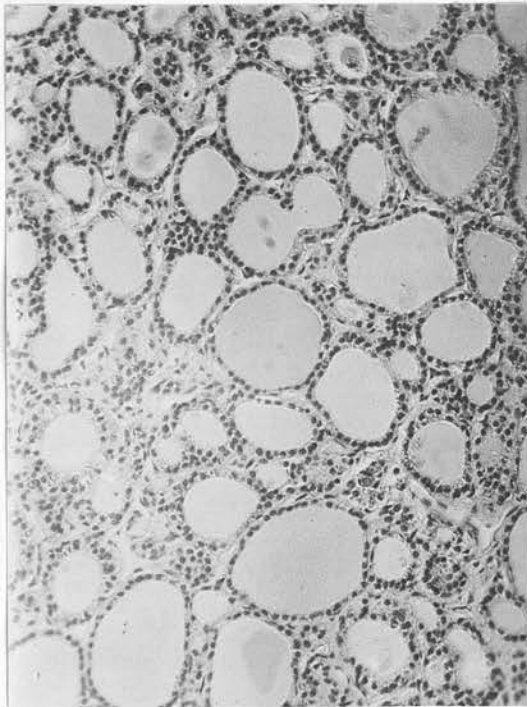
C.

HORSE.

Right Cervical Sympathetic
Section.



LEFT THYROID. X90

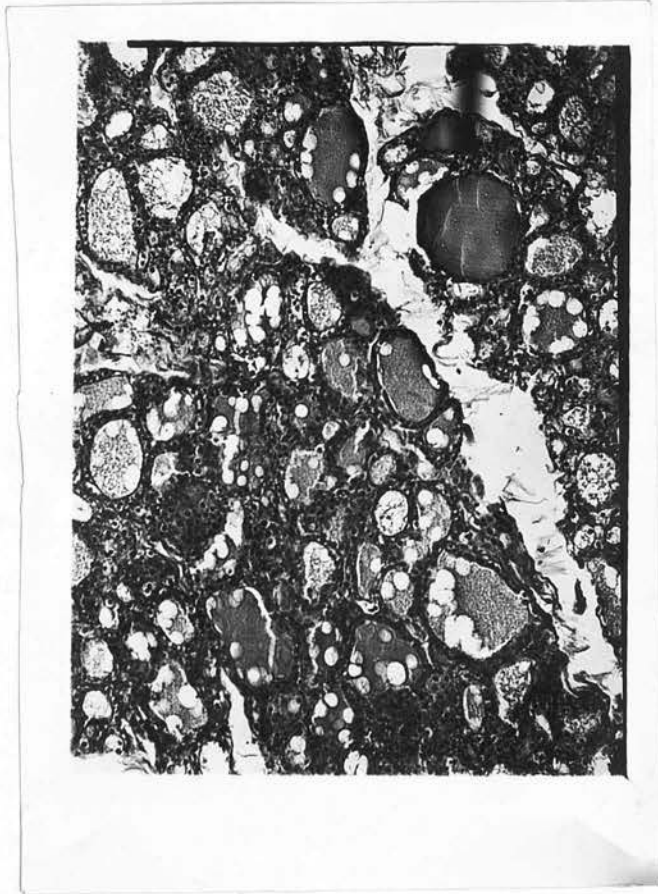


RIGHT THYROID. X90

D.

THYROID GLAND OF CAT.

SUPERIOR CERVICAL GANGLIA HAD BEEN
PREVIOUSLY RESECTED.



X 110.

EFFECT OF THYROID AUTACOIDS ON NERVE.

The general symptoms which present themselves as a result of feeding with thyroid suggest that the autacoids of the gland affect the nervous system. The increased basal metabolism, the rapid heart beats, the dilated pupils, and the condition of activity of the sweat glands which are produced suggest a stimulation of the sympathetic system. Dilatation of the blood vessels, accompanied by a low blood pressure, also occurs, and suggests not a sympathetic stimulation, but the reverse. In addition to these symptoms, referable to the autonomic system, twitchings of muscles, mental excitement, and exaggerated reflexes are met with, and suggest an action of the autacoids on the central nervous system.

Asher states that thyroid extract causes an increased sensitivity of the vagus, depressor, and splanchnic nerves. His method of investigation was to expose the depressor nerve and find the smallest electrical stimulus necessary to cause a fall of blood pressure. His results were not constant in cats and he therefore used rabbits. It is of

importance to note that the extent of the fall is no criterion, for this was found to vary even with the same strength of stimulus and the same experimental conditions. The necessary stimulus being found, the superior laryngeal nerves were stimulated - or an injection of gland extract administered - and after a suitable interval, the stimulus necessary to produce a fall of pressure again found. Working in this way, Asher found that the effect of thyroid secretion was to cause a greater fall of pressure on stimulation of the depressor. Similar experiments were carried out on vagus and splanchnic nerves, with a similar result.

A number of points have to be noted in connection with the investigation. The results obtained in testing the excitability of the depressor vary. Weak stimuli must be used - the best results being obtained with 30-100 K.U. - in such cases the response remains constant for a long period; whereas with strong current one cannot obtain a constant effect. The response is very sensitive to temperature, and even to such influences as sound and light. Asher found that noise occurring during the experiment influenced results, as also did even the passage of a shadow over the field of operation.

Cyon found that iodothyrene sensitised the depressor. This Asher and Flack were unable to confirm: they consider that there is much doubt as to whether this substance is an active principle in thyroid secretion. Oswald⁽⁹⁸⁾ states that thyroglobulin and other organic iodine compounds increase the sensitivity of depressor, vagus, and sympathetic in the dog, and that the activity in this direction varies with the iodine content of the substance.

Levy⁽⁹⁹⁾ was unable to confirm the results of Asher. He found that excitation of the nerves to the thyroid (sympathetic) caused an increased sensitivity to adrenalin, as measured by rise of blood pressure, but was unable to obtain at the same time any evidence that the vagus was more sensitive to electrical stimulation. Like Asher, he used the smallest stimulus (K.U.) necessary to produce a fall of blood pressure, as an indication of the sensitivity of the nerve. In view of Levy's experiments, Asher's results cannot be accepted as conclusive.

Levy further⁽¹⁰⁰⁾ investigated the question by studying the effect of thyroid secretion on the excitability of the cardiac vagus, since it is found that in cats pithed to the level of the third

thoracic segment, stimulation of either vagus with a given strength of stimulus produces a uniform degree of depression. His results were negative.

The action of the thyroid autacoids on the central nervous system is very striking. Removal of the thyroid leads to a depression of all the functions of the nervous system, idiocy resulting. Administration of thyroid extract to a cretin produces an improvement, and usually a complete recovery of mental function. The mode of action is unknown, but thyroxine has the same effect, and accordingly may be looked upon as the autacoid concerned. Mott has observed that in persons suffering from hypothyroidism there is widespread chromatolysis in the cells of the cerebral cortex.

Many conclusions regarding the action of thyroid secretion on nerve have been based on observations - mainly clinical - of the phenomena in exophthalmic goitre. These observations cannot be admitted as evidence, for there is no proof that the disease is the result of a simple oversecretion of the thyroid: the secretion may be not merely excessive, but abnormal, and further, as we have seen above, physiological experiments have proved an interrelation between thyroid and suprarenal activity

and their autonomic innervation.

It is important to note that Levy⁽⁹⁹⁾ found that the increased effectiveness of adrenalin as a pressor agent after stimulation of the thyroid is not dependent on a greater amount of circulating adrenalin, but rather is due to a sensitization of the sympathetic structures concerned. This would indicate that in exophthalmic goitre there is no reason to suppose, as some have done, an increased amount of adrenalin in the circulating blood to explain the syndrome of sympathetic over-excitation.

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