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REPORT XCIII.

THE ACTION OF ADRENALIN.*

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ADRENALIN, apart from its general poisonous properties that are manifested when large quantities are introduced into an animal, has a quite specific power of stimulating plain muscle and gland cells. Attention to this fact was first drawn definitely by Langley.¹ He pointed out that only those plain muscles are stimulated by adrenalin which are supplied with sympathetic nerves, and that broadly the reaction is similar to that caused by electrical excitation of these nerves. The work referred to in this report establishes the generalization.

A. STIMULANT ACTION OF ADRENALIN.

1. Law Governing the Reaction of Plain Muscle to Adrenalin.

Gaskell² gave the first broad classification of the nerves efferent from the brain and spinal cord. He showed that while the motor nerves to striped muscles connected with the skeleton issue in all the anterior roots, those to the unstriped muscle of the blood vessels and viscera and to gland cells do not flow out in a continuous series of anterior roots down the length of the spinal cord, but in three divisions, which are separated one from the other by the nerve roots of the fore and hind limb plexuses. These visceral nerves all bear ganglia on their course from spinal cord to peripheral tissue. Langley has introduced a fresh nomenclature, according to which the entire group of ganglionated visceral nerves is styled the autonomic system; in this are the three subdivisions of the cervico-cranial, the thoraco-lumbar, and the sacral root outflows. The thoraco-lumbar root outflow is also called the sympathetic. Plain muscle is often innervated from two of these sources, and then the double innervation is antagonistic. In all cases the reaction to adrenalin is found to be identical with that to electrical stimulation of the sympathetic (thoraco-lumbar) nerves. (Cf. diagram.)

Bladder.—The bladder of the cat is inhibited both when adrenalin is injected into the circulation and when applied directly to the bladder wall. But the urethra, that is the sphincter of the bladder, is at the same time powerfully constricted. Excitation of the hypogastric nerves has the same results. Similar movements are seen in the bladder and urethra of the monkey, *Macacus rhesus*. But the bladder in the dog and the rabbit is unaffected by adrenalin and by the hypogastric nerves; and that of the ferret and the goat is thrown into complete contraction by both these means.

Thus all three possibilities of response to adrenalin are instanced in the various types of mammalian bladder, and in each in strict accord with the nature of the sympathetic innervation. All these bladders, of course, also receive motor nerves from the sacral visceral outflow, and the urethra inhibitor nerves.

Heart.—In every vertebrate examined the beat of the auricles is both augmented and accelerated. Over-distension of the heart chambers in the face of the great rise of blood pressure may, however, give rise to reflex slowing and so mask the true action of adrenalin. But whereas the ventricle also of the mammal is stimulated to greater beats, that of the tortoise and of the pigeon is unaffected. This agrees identically with the differing extent of sympathetic innervation in the different species. The coronary vessels in the cat are slightly dilated by the drug, though arteries in other organs are constricted.

Alimentary Canal.—The stomach is inhibited. This, too, despite the counter-statement of Page May,³ is proved to be the result of stimulating the sympathetic nerves in the cat. In mammals the entire length of small and of large intestine is inhibited by adrenalin, except where it tightens with a power varying in different species the grip of the pyloric, ileocolic, and internal anal sphincters. The parallel action of adrenalin and sympathetic nerves holds, though the scheme

of innervation alters, when one passes to study the intestines of the bird and amphibian. The proximal part of the pigeon's small intestine is thrown into contraction by adrenalin. Dixon⁴ has shown that the same is the case with the frog's stomach. As in the mammal, the caeca and colon of the bird are relaxed.

Apparent Exceptions.—Chief of these are the skin muscles moving the hairs and the dilator pupillae. The hairs down a cat's back and tail rise stiffly when their nerves are stimulated; their motion is but slight when adrenalin is injected. In other animals the corresponding movement is greater. The hairs on the tail of a mongoose are very readily excited by adrenalin. It would seem, then, that the delicacy of reac-

Diagram of the nerves efferent from the central nervous system in the mammal.—D, the non-ganglionated ordinary motor nerves to striped muscle. On the left side these are omitted for simplicity, and only the ganglionated visceral (autonomic) nerves to plain muscle are indicated. Of these, A is the cranio-cervical outflow (for example, vagus); B, the thoraco-lumbar or sympathetic; C, the sacral outflow (nervus erigens to bladder, colon, etc.). All these three subdivisions contain both motor and inhibitor nerves. B1 is the sympathetic ganglion cell, B2 the paraganglion cell containing adrenalin (that is, medullary cells of the suprarenal). The black rectangle innervated by the fibres of the cells B1 also represents the tissues which alone are stimulated by adrenalin—that is, by the secretion of the cells B2.

Afferent sensory nerves and their posterior root ganglia are all omitted from the diagram.

tion to adrenalin varies directly with the functional use of the muscle by the animal in the reflexes of daily life. Kipling has made familiar the fact that the mongoose, Rikki-Tikki-Tavi, expresses every emotion by fluffing out its tail. A similar explanation is applicable to the dilatation of the pupil. This is readily produced in the cat; in the dog, rabbit, and goat it is generally feeble and overpowered by the constriction caused by central stimulation of the third nucleus. Though the excitability by adrenalin varies with functional use, there is not a proportional variation in the direct electrical excitability of the sympathetic nerves to the muscle. So the

* A paper, giving the experiments in detail, is published in the *Journal of Physiology*, xxxii, 1905.

following law seems to be true for all vertebrates: That the reaction to adrenalin of any plain muscle in the body is of a similar character to that following excitation of the sympathetic nerves supplying that muscle, and the extent of the reaction varies directly with the frequency of normal physiological impulses received by the muscle in life through the sympathetic nerves.

2. Localization of the Action.

Nerve cells and their processes, whether in or out of the spinal cord, are comparatively inexcitable by adrenalin. Section of the nerves, after sufficient time has been allowed for the severed nerve to decay as far as its ending in connexion with the muscle, leaves the muscle even more responsive to adrenalin, whether to contraction or relaxation,

than it was before. Therefore the stimulation must be effected directly at the periphery.

But certain poisons* can block the stimulation by adrenalin and by the sympathetic nervous impulse, while leaving intact all other irritability of the muscle, and even opposing no obstacle to the passage to it of the antagonistic nervous impulse. Plainly these poisons do not affect the muscle fibre itself, but some intermediate substance between the sympathetic nerve and the contractile fibre. All other chemical stimulants, which are known to excite plain muscle directly, evoke from all the plain muscles of the body reactions every-

*Apocodeine, the action having been discovered by Dixon and the argument applied by Brodie and him (*Journ. of Physiol.*, xxx, p. 494, 1904). Also chrysotexine, discovered by Dale (see *Proc. Physiol. Soc. in the Journ. of Physiol.*, May, 1905).

Table summarizing all the established actions of adrenalin. because little is known yet of their double innervation. tracheal glands are excited by

It deals only with plain muscle, gland cells being omitted Langley discovered that the salivary, lachrymal and the drug to lively secretion.

	Action of Adrenalin.	Visceral Nerves.		
		Sympathetic (or thoracico-lumbar)	Cranial.	Sacral.
<i>Heart.</i>				
Auricle	beat accelerated and augmented	same	inhibition	—
Ventricle :				
Mammal	beat augmented	"	"	—
Amphibian	"	"	"	—
Pigeon... ..	no effect	"	no effect	—
Tortoise	"	"	"	—
Coronary arteries (Mammal)	dilatation	"	(?)	—
<i>Arteries and arterioles.</i>				
Of submaxillary gland and buccal mucous membrane	constriction	"	dilatation	—
Of lungs	no effect (?)	"	—	—
Of external generative organs	constriction	"	—	dilatation
Generally, reaction varying in different tissues and different animals	"	"	—	—
Of spleen	contraction	"	no effect	—
<i>Alimentary canal.</i>				
Oesophagus (mammal)	inhibition	same (?)	contraction	—
Cardiac sphincter (rabbit)	"	"	contraction and inhibition	—
Stomach :				
Cat and rabbit	"	"	inhibition of fundus, then full contraction	—
Bird	(?) not contraction	inhibition	contraction	—
Frog	contraction	same	(?)	—
Pyloric sphincter (rabbit)	"	"	contraction and inhibition	—
Gall bladder	inhibition	"	contraction	—
Gall duct	contraction	"	(?)	—
Small intestine :				
Mammal	inhibition	"	contraction	—
Bird	contraction	"	(?)	—
Ileo-colic sphincter	"	"	no effect	—
Colon and caeca (mammal and bird)	inhibition	"	—	contraction of terminal part (bird ?)
Internal anal sphincter :				
Rabbit	"	"	—	quick relaxation
Cat and dog	contraction	"	—	variable
Bird	"	"	—	(?)
<i>Lung.</i>				
Muscles of bronchioles	no effect	"	contraction	—
<i>Urinary tract.</i>				
Bladder :				
Cat and macaque	inhibition of body	"	—	contraction
Dog and rabbit	indifferent	"	—	"
Ferret and goat	contraction	"	—	"
Urethra (mammals)	"	"	—	relaxation
Ureters	contraction (?)	same (?)	—	(?)
<i>Internal generative organs.</i>				
Uterus and Fallopian tubes	"	"	—	no effect
Vesiculae seminales and vasa deferentia	"	"	—	"
<i>External generative organs.</i>				
Retractor penis	"	"	—	relaxation
Auto-genital skin muscles	"	same (stronger)	—	inhibition
<i>Arrectores pilorum.</i>				
Mammal	contraction (variable)	"	—	—
Bird... ..	" (weak)	"	—	—
<i>Eye structures.</i>				
Nictitating membrane	withdrawn	same	protruded (?)	—
Eye-lids	opened	"	(?)	—
Pupil... ..	dilated	same	constricted	—
Eye-ball	protruded	(usually stronger) same	turned inward	—

where of like nature, though it may be of greater or of less extent. It is the peculiarity of adrenalin to excite contraction here, relaxation there, and always in identical agreement with the response to the sympathetic nervous impulse. So it cannot be the plain muscle as such which is immediately stimulated by the drug. It must be a mechanism developed out of the protoplasm of the muscle cell, when the latter is in continuity and functional union with a sympathetic nerve axon. This mechanism, the myoneural junction, serves to transmit the impulse to the muscle, and probably determines whether the response of the latter shall be that of inhibition or contraction. In lack of such connexion, as in the ventricle of the tortoise or the bladder of the dog, the muscle is indifferent to adrenalin.

This characteristic reaction to adrenalin marks the deep distinction between the myoneural junctions of the sympathetic (thoracico-lumbar) nerves on the one side, and all the remaining visceral nerves on the other. It embraces the less difference between contraction and inhibition in its own group, and attaches to muscles morphologically differentiated so far asunder as those of the rhythmically pulsatile heart and the tenaciously constricting urethra. By the test, it is revealed a biochemical peculiarity of the entire mass of muscle united with sympathetic nerves.

How the muscle forming the wall of a viscus originally obtains its connexion with sympathetic nerves is a problem as yet unsolved by morphology; but given such connexion, it seems that the change in muscular tension evoked by the nervous impulse is then determined simply by functional need of co-ordinated activity. Where quiet lodgement of the visceral contents is required, as in the cat's bladder, the gall bladder, in the small and the great intestine, there the sympathetic nerves inhibit the body of the viscus and constrict the sphincter closing exit. Adrenalin does the same.

B. TOXIC ACTION OF ADRENALIN.

It was early discovered that the subcutaneous injection of suprarenal extract caused death; and the discovery led to the view that the suprarenals are concerned with the removal of poisonous substances from the body. For removal of the glands was fatal, and equally so was the injection of their extract. But death results only when the amount injected is large—greatly in excess of all the adrenalin stored at any moment in the suprarenals of the animal.

Reverting for a moment to the phenomena of muscle excitation by adrenalin, it should be noted that the stimulation passes off very quickly, but can be renewed again and again by fresh injections. The adrenalin disappears—for the main part actually in the tissues which it excites—and the sympathetic nerves are made neither less nor more excitable by its action.

When large quantities are injected *intravenously*, the excitatory effects persist for some time until the adrenalin has thus disappeared. Later the animal dies. By French⁵ workers the fatal dose for injection within the blood stream has been determined to be 0.2 mg. per kilogram body weight for the rabbit and dog, and 0.5 to 0.8 mg. for the cat.

Subcutaneous injection is not attended by the phenomena of stimulation except in the neighbourhood of the point of injection. Unless there is rapid flow of lymph from that area to the thoracic duct and thereby to the blood stream, absorption is so slow that the adrenalin disappears as rapidly as it enters the blood, and never attains the concentration needed to stimulate. It does, however, enter the circulation as adrenalin, for whether given beneath the skin or by the mouth,⁶ it can stimulate tissues that have been denervated and so rendered more excitable. Quite small amounts cause hyperglycaemia and diabetes.⁷ Twenty milligrammes beneath the skin do not affect a rabbit for the first half-hour. Then paralysis and lethargy develop, and at the end of an hour the animal is dead. The typical reaction of plain muscle to adrenalin never appears. Death, therefore, cannot have been caused by extraordinary rise of blood pressure. It is in the rabbit asphyxial owing to oedema of the lungs and nervous paralysis. This nervous paralysis is always a conspicuous feature of adrenalin poisoning. A similar dose will not kill a cat, though producing ultimately inflammation of the kidney and liver.

As a subsidiary point it may be noticed that very small quantities—for example, 3 mg.—introduced into the blood of a dog may kill it by inducing at once intravascular coagulation.

C. FUNCTION OF THE SUPRARENAL GLANDS.

In regard to this question no very conclusive experiments have been performed, and only a preliminary account of their general tenor can be given.

Adrenalin was proved by Oliver and Schäfer⁸ to occur only in the medullary, and not in the cortical, cells of the suprarenal. Cells of precisely the same histological character, and apparently the same embryological derivation, exist in lower vertebrates throughout the body in close association with the cells of the sympathetic ganglia. In the mammal they are massed in the suprarenal, but vestiges of the wider distribution remain; of these the intercarotid body is an example, being associated with the superior cervical ganglion. Kohn⁹ has consequently named these cell masses the paraganglia. They too, wherever occurring, contain adrenalin.¹⁰

Without doubt, then, it may be stated that there are two related types of cell in the vertebrate:

1. The sympathetic ganglion cell, which is united with the plain muscle by its axon process and provides a path for the nervous impulse.

2. The paraganglion cell, which is not in connexion with the muscle (though most richly supplied with nerves and blood vessels), but secretes a chemical substance into the blood that can produce an identical excitation of the muscle through its myoneural junction. These cells (1) and (2) are as brother and sister to one another, being in the closest kinship of morphological parentage.

Removal of the suprarenal glands—that is, of the mass of cells (2) together with the cortical cells—is always fatal. Death comes rapidly, in 15 to 70 hours after the operation in the cat. The blood pressure falls, lethargy and weakness increase, and with heart failure life ends quietly. The English-bred guinea-pig cannot survive for many hours the extirpation of even one gland.

But the nervous tone of the musculature innervated by the sympathetic nerves, may be abolished by removal of the spinal cord from the first thoracic to the fourth lumbar segment; and yet the animal lives. Similarly the peripheral ganglia of these nerves (both superficial cervical, stellate, semilunar, renal, and inferior mesenteric ganglia) may all be excised in a single operation without a fatal issue.

Therefore in the cortical and medullary cells of the gland must inhere some peculiar activity, on which essentially depends the maintenance of tone of the sympathetic nerve and muscle system. The chemical extractives of these glands are more necessary for this tone than the integrity of the nervous union with the central nervous system.

Of chief moment in the general failure consequent to removal of the glands is that of the muscles of the circulatory system. With their activity depressed life soon is ended. But it is to be noted that in extreme fatigue, and in many infectious diseases—for example, diphtheria and typhoid fever, the medullary cells are emptied of adrenalin and function ill. Delayed restoration of strength is then in part due to the poisoning of these glands. And Addison's disease is but an extreme instance of their pathological lesion. They and their secretion are of essential importance to the machinery of life.

The opinion outlined above rests on no facts that definitely point to a therapeutic use of adrenalin. In large doses it is dangerous. Small amounts given beneath the skin cause no stimulation except at the point of application; they would, therefore, on this count, be useless to check hæmoptysis, quite apart from the proof given by Brodie and Dixon¹¹ that the lung vessels are not constricted by adrenalin. But what adrenalin can do in promoting tone of the muscles, though never actually present in such concentration as to stimulate them, is unknown. Hence clinical administration must be empirical.

Many writers have described tumours of the suprarenals. It is desirable to know whether in some cases these contain true medullary cells. The presence of adrenalin in them, or in suprarenals examined after death caused by various diseases, may be roughly determined by a simple test—that described first by Henle in 1869. Paraganglion cells containing adrenalin stain a dark-brown colour, bright yellow in thin sections, when the tissue has been placed in any solution of chromic acid salts—for example, Müller's solution. Best is perhaps a mixture of 90 per cent. $K_2Cr_2O_7$ (3.5 per cent.) with 10 per cent. commercial formaldehyde (40 per cent.). The stain washes out very slowly; but it is useless to examine a tissue later than twenty-four hours after death, because adrenalin disappears early in the *post-mortem* changes. For the opportunity to examine several suprarenal glands so

prepared I am already indebted to the kindness of Mr. L. Noon, F.R.C.S., of St. Bartholomew's Hospital. The question merits the attention of pathologists.

REFERENCES.

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MEMORANDA:

MEDICAL, SURGICAL, OBSTETRICAL, THERAPEUTICAL, PATHOLOGICAL, ETC.

DIACHYLON AS AN ABORTIFACIENT.

IN reference to your notice in the BRITISH MEDICAL JOURNAL of the 8th inst. on the use of lead as an abortifacient and the fact that in the cases recorded by Dr. Ransom wrist-drop did not occur, I recently attended a case in conjunction with my colleague, Dr. Barton, where the presence of this symptom enabled us to arrive at a correct diagnosis.

My patient aborted in the month of February last and denied having taken any drug, but having amenorrhoea the following months of March and April, repeated her doses of diachylon pills.

When called in again on April 17th, I found all the cardinal symptoms of plumbism—including wrist-drop—markedly present.

On questioning the patient closely, I then ascertained the history of three months' lead administration.

In Dr. Ransom's cases it is probable that only one large initial dose was taken, and that coming under appropriate treatment, the drug was eliminated. To bring on the typical nerve lesions, a short continuation is required.

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UNDULANT FEVER IN SOUTH AFRICA.

THE subject of Mediterranean or Malta fever is at present receiving a good deal of attention, and a considerable number of contributions upon it have appeared in the pages of the BRITISH MEDICAL JOURNAL during the past six months. It does not appear to be generally known outside of South Africa that a disease apparently identical with Malta fever is endemic in certain parts of this country. I send herewith for your perusal a copy of a paper* by me on "The Question of the Presence in South Africa of Undulant or Malta Fever" read before the Orange River Colony Medical Society in April, 1904. The paper was published in the *South African Medical Record* of August 15th, 1904, and was based upon a study of seventy-two cases during a period of eighteen months, presenting the clinical features of undulant fever.

On February 8th, 1905, I read a second paper on the subject before the Orange River Colony Medical Society. In that paper I recorded the following facts:—

Among the original seventy-two cases I observed sixteen cases of joint swellings, although at the time when I wrote the first paper, I was able to cite only four. There was hearsay evidence of several more cases of joint swellings at distant farms.

Blood samples from thirty-four of my patients were sent to the Cape Colony Government laboratories at Grahamstown and at Capetown. The tests were conducted by Dr. Edington and Dr. G. W. Robertson, who kindly procured cultures of the *M. melitensis* for the purpose. The following were the results:—

Dilution used—	Positive reaction to Malta fever.	Negative.
1 in 10	3	—
1 in 20	6	—
1 in 30 to 35	8	3
1 in 50	4	2
not stated	4	—
Total	25	5

Positive reaction to typhoid fever, 3

One, which was negative to Malta fever, was not tested for typhoid. The four latter were comparatively short fevers presenting the characteristics of typhoid.

In the *South African Medical Record* of October, 1903, a paper on "Camp Fever" by Mackenzie, of Kimberley, was published.

* It has been placed in the library of the Association.

In that paper Dr. Mackenzie gave it as his opinion that this fever had its closest analogue in Malta fever. From Dr. Mackenzie's description of "camp fever" I am led to believe that it is the same as that which has been prevalent in my practice, and consequently that the disease is not a new importation due to the circumstances attending the late war; for I understand that the term "camp fever" has been in use in Kimberley from the early days of the diamond fields.

Last February I sent a patient for observation to the Government Hospital at Bloemfontein. Dr. Targett Adams, Government bacteriologist, reported to me that the *M. melitensis* was undoubtedly present in the patient's blood.

Philippolis, O.R.C.

P. D. STRACHAN, M.A., M.B., Ch.B.

LARGE VESICAL CALCULUS.

CAPTAIN H. A. WILLIAMS, D.S.O., I.M.S., Resident Medical Officer, General Hospital, Rangoon, has just forwarded me the final result of a case of stone in the bladder operated on by me in February. He has at the same time called my attention to the report in the BRITISH MEDICAL JOURNAL of January 7th, by Mr. Pike, of St. Vincent, of the successful removal entire of a stone weighing 13½ oz.; to a note by Lieutenant-Colonel Hatch, I.M.S. ret., of a stone removed entire by him weighing 17 oz. (result not stated); and to a note by Major Tilson Hudson, I.M.S., in the JOURNAL of March 18th of a fatal case of stone weighing about 20 oz. removed after bisection.

My case was that of a Burman cultivator, aged 37, who had suffered for fifteen years from symptoms of stone in the bladder. His general condition was, however, surprisingly good, although there was constant dribbling of urine, which was intensely fetid. Litholapaxy being found impossible on account of the size of the stone and the way in which it filled the bladder, suprapubic cystotomy was performed, and the stone was then crushed, with great difficulty, by a lithotrite introduced through the suprapubic wound. The operation occupied two hours, and was extremely tiring. The fragments of the stone weighed, when dry, 13 oz. 6 dr. Its central part was extremely hard, and was surrounded by softer white concentric laminae, fragments of the outer giving a good idea of its size. The wound was left open. The patient had no bad symptoms, and was discharged with his wound healed just a month after.

The most important point in connexion with these large stones would seem to be the best means of removal. Removal entire is the most expeditious way, but this means a very large incision into the bladder, with the danger of opening the peritoneum, and the exercise of perhaps a dangerous amount of force. Removal by crushing means a prolonged operation in a patient generally greatly debilitated, and a considerable amount of injury to the mucous membrane of the bladder. I have no experience of perineal litholapaxy and its applicability to these cases.

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HYPERPYREXIA.

ON March 31st, 1905, about 10.30 p.m., I was asked by a lady to see her nursery governess. She informed me that she had taken the patient's temperature under the arm; the first thermometer that she used burst, and the second registered 110.2° F. I found the patient in bed with flushed face, quick pulse, complaining of pains in the back of the head, pains in the eyeballs, pains down the back and legs, and, as she expressed herself, she was all pains. On taking the temperature with my own thermometer (Kew certificate) I found that it likewise registered 110.2° F. in the axilla.

I looked upon the case as one of acute influenza in a neurotic subject, ordered quinine sulphate gr. vi every second hour and a diaphoretic mixture. The next morning I found her a great deal better, with temperature almost normal; it remained so until April 2nd, when I again had a message late at night; then her temperature had registered 112.3° F. There was considerable restlessness and delirium, with dilated pupils. The quinine was repeated in the same dose. The nurse in attendance put her into a hot bath and administered stimulants freely, and when she had been put back to bed free perspiration set in, saturating everything about her. When I saw her next day the temperature had fallen to normal, and remained so, with the exception of a slight increase about a week after, which could be easily accounted for; she was given a mixture of dilute hydrochloric acid, quinine, liquor strychninae with the glycylo-hypophosphates.