"THE INNERVATION OF THE BLADDER AND URETHRA[1]." By T. R. ELLIOTT, *George Henry Lewes student.*

(From the Physiological Laboratory, Cambridge.)

CONTENTS.

PART I.

PART I.

To determine the nervous control of the bladder with its simple structure and single function might seem no hard task. Yet some of the main facts are still disputed. The original discoveries by

[1] Toward the expenses of this research grants were received from the Government Grant Committee of the Royal Society.

Budge[1], and by Gianuzzi[2] in Claude Bernard's laboratory, that impulses to contraction can reach the bladder by either of two paths, through the lumbar spinal roots in the hypogastrics, or through the sacrals in the pelvic visceral nerves, have been confirmed by all subsequent workers. Von Zeissl (1893) suggested a new enquiry, whether the bladder in obedience to the theory of crossed innervation did not receive also inhibitor nerves for the longitudinal muscular coat by the sympathetic or lumbar roots. By varied experiments on one animal, the dog, he convinced himself of their existence; and also of the corollary that the sacral nerves inhibit the sphincter. Langley and Anderson (1895), examining afresh an observation in which Langley (1890) had preceded von Zeissl, were able occasionally to demonstrate lumbar inhibition of the cat's bladder, but concluded that such inhibitor fibres were few in number. Repeating their observation, Stewart (1899) without reserve affirmed the existence of lumbar inhibiting nerves. Since then workers have recurred to the oldest view, Rehfisch, Fagge, and Wlasow maintaining that only motor nerves exist for both the bladder and its sphincter.

The experiments of this paper[3] reconcile most of these differing observations by showing that the innervation of the bladder varies from animal to animal, and that the error was the old one of arguing from the particular to the universal. Beyond this reconciliation lies a greater interest. The biochemical test by adrenalin has marked the deep distinction between the muscle mass connected with the sympathetic nerves and that controlled by the sacral visceral nerves. Both occur in the bladder. Its study must suggest something of the laws controlling the development of each.

I. THE CAT.

Methods. As any direct record of linear movements in the bladder wall involves some exposure, and so increases the difficulty of demonstrating inhibition, I preferred the natural method of recording changes in the fluid contents of the bladder. For comparison with one another these changes must be roughly measured; and to determine from them the actual tension of the bladder wall requires that a clear distinction be drawn between volume changes and pressure changes. Both will be

[1] *Virchow's Archiv*, xv. p. 115. 1858.

[2] *Journal de la Physiologie*, vi. p. 22. 1863.

[3] All the animals used were anæsthetised unless or until the brain was destroyed.

influenced by the muscular tension. One of the variables must therefore be kept approximately constant, while change is imposed on the second.

For *pressure* changes the bladder was emptied, then filled with a known volume of saline solution at 38° C., and connected with a water manometer of small bore. The air above the surface of the water column was connected with a small Brodie bellows recorder, and so a continuous tracing of roughly isometric changes on a constant volume was obtained.

For *volume* changes a large graduated reservoir was substituted for the manometer. This gave any height of water pressure needed; and the air in the closed system above it was in turn connected with a large bellows recorder. The graduations on the reservoir served to check the accuracy of the bellows. No care was taken to maintain the water external to the bladder at the body temperature, for warming the walls of the reservoir caused expansion of the recording volume of air above the water, and it did not seem worth while to complicate the apparatus by introducing a source of heat into the water itself. Pressure records avoided this fault.

The intravesical pressure alone does not completely represent the tension of the enveloping muscular wall. This tension, if the bladder be regarded as a sphere with elastic walls,

$$= \frac{\text{intravesical pressure} \times \text{radius}}{2 \times \text{thickness of wall}}.$$

With increasing distension of the thin wall, its thickness varies inversely as the square of the radius: that is, the tension $\propto P . r^3$.

Or, since the volume $= 4/3 . \pi . r^3$, the tension varies as the product of the volume and the pressure ($T \propto V . P$).

Increase of volume will therefore augment the tension. A given change of muscular tension will produce a greater change of pressure in a bladder moderately distended than when it is excessively filled. Furthermore contraction of the fibres at the base of the bladder, where the radius of curvature is small, will have a disproportionately large effect in raising the intravesical pressure.

Pressure changes give a closer representation of the changes in muscular tension, to which is probably to be attributed the micturition reflex; and moreover it is under such isometric conditions that inhibition plays its part. But practically it was found to be more convenient to record volume changes, which are simply as the cube of the linear shortening or elongation of the muscle fibres under conditions that are very roughly isotonic. These could be followed with a bladder enclosed in the abdomen, for they were virtually unaffected by movements of adjacent viscera. The initial values of intravesical pressure, *p*, and of volume, v, are stated in all the experiments, and serve to indicate the tension of the muscle at which the changes in length took place. This tension may be regarded from some points of view as being at any moment the sum of two components, physical and physiological. The latter, the "tone" impressed by nervous ties, often drops to zero when the sacral nerves are cut, and then of course inhibition cannot be demonstrated. In most of the experiments a distending pressure of 15 cm. water was employed.

For a volume record the bladder often was not exposed. A catheter was inserted by the urethra from the ext. meatus, or in the male from below the prostate after splitting the symphysis: generally a ligature was tied around the urethra. The hypogastric nerves[1] were found by a lateral incision at the edge of the quadratus lumborum, so that the peritoneal cavity was not opened. In all animals but the dog and rabbit I found it to be possible to dissect out the pelvic visceral nerves (nervi erigentes) also without exposure of the bladder. For this purpose an incision was made at the root of the tail well above the anus; the recto-coccygeus muscle was transected, and then the fibrous tissue between the rectum and the caudo-coccygeal muscles torn away until the nerves were discerned on either side 4 or 5 cm. up the tunnel. They are found with their accompanying blood vessels in a small mass of fat, each arising generally as a single compact bundle from the sacral plexus. Both nerves were stimulated simultaneously, a crossed wire being used to connect the electrodes. Fine shielded electrodes were of course needed. I used a special pattern with one wire on the curved shield and the second on the moving plunger, so that the nerve lay with the wires on either side of it and was more satisfactorily stimulated.

The Hypogastric Nerves.

Motor fibres to the cat's bladder were recognised in the hypogastrics by Sokownin[2] in 1874, Nussbaum[3], Nawrocki and Skabitschewsky[4], and by Sherrington[5]. Langley and Anderson[6] noticed that the movement was chiefly of the base of the bladder; but following up the earliest observation on the presence of inhibitor nerves

[1] The nomenclature used in this Paper for the various nerves may be gathered from the summarised statement on p. 411.

[2] *Pflüger's Archiv*, VIII. p. 600. 1874.

[3] Reference in Hoffmann und Schwalbe's *Jahresberichte*, VIII. Abth. p. 64. 1880.

[4] *Pflüger's Archiv*, XLVIII. p. 335. 1891.

[5] This *Journal*, XIII. p. 676. 1892.

[6] This *Journal*, XIX. p. 73. 1895.

made by Langley[1] in 1890, concluded that these nerves contain few or no inhibitor fibres. Stewart[2] placed the existence of such inhibition beyond doubt.

Stimulation of these nerves, the central ends having been cut to avoid reflexes, has always a double effect. First is a rapid contraction expelling generally 4 to 5, at the most 8, c.c., under 15 cm. pressure: inhibition immediately ensues, so that the curve of contraction is sharply cut down (cp. Fig. 1 and Fig. 13), and the bladder relaxes

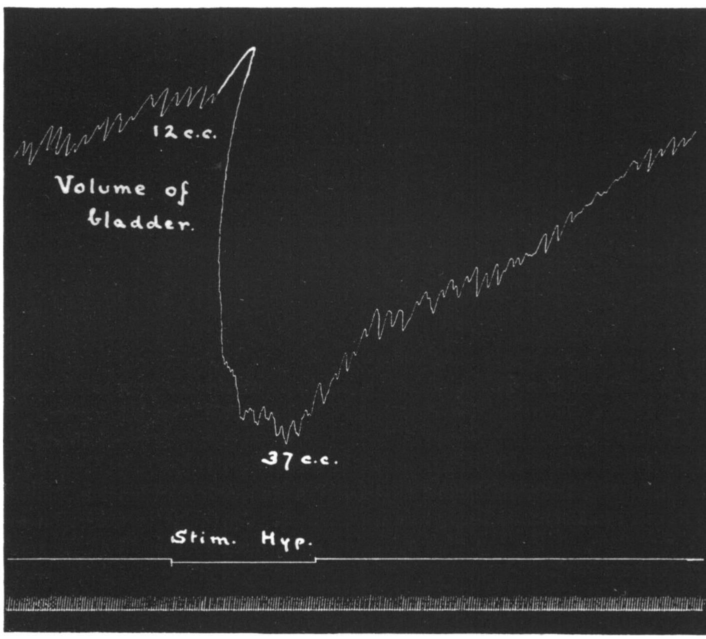


Fig. 1. Inhibition of the cat's bladder by stimulation of the hypogastric nerves; isotonic *volume record.* Albino cat, blue eyed and deaf. Ether. Tone of bladder high, v. 12 c.c., p. 15 cm., as pelvic visceral nerves were uncut.

Stim. hyp., coil 7 cm.: bladder contracts 5 c.c., then relaxes 25 c.c., with rapid recovery as soon as stimulation ceases.

to the extent of it may be 30 c.c. from a vol. of 30 c.c. Fig. 2 illustrates the corresponding fall of pressure with constant volume. In the latter case the results recorded on the tracing vary with the pressure used. Thus in one Exp. with a vol. of 40 c.c. and p. 15 cm. the hypogastrics produced a rise of 10 cm.; but with vol. 60 c.c. and

[1] This *Journal*, XII. 1890. *Proc. Physiol. Soc.* p. xxxii.

[2] *American Journ. Physiol.* II. p. 182. 1899, and III. p. 1. 1899.

p. 35 cm., the tension of the wall being therefore nearly quadrupled, a fall of 10 cm.

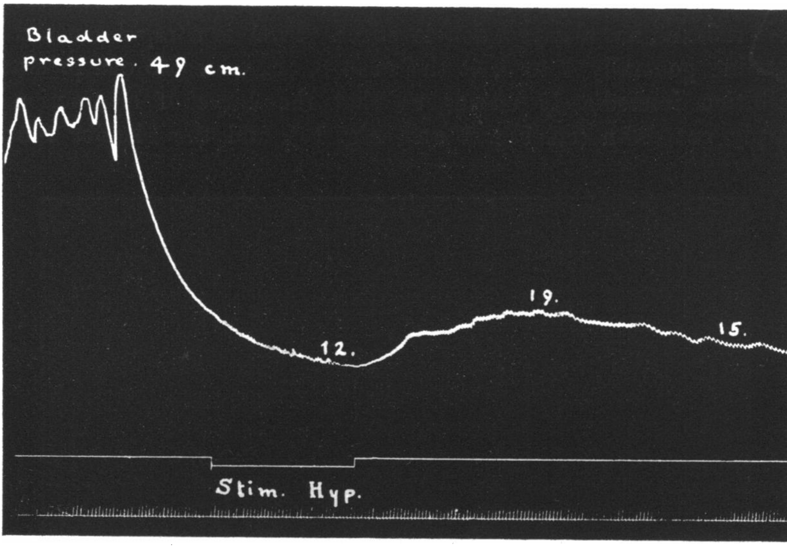


Fig. 2. Inhibition of the cat's bladder by the hypogastric nerves: isometric *pressure record*. Ether. Hypogastrics cut, but not the pelvic visceral nerves. Tone of bladder high: constant volume of about 15 c.c. Pressure changes in cm. of water read on manometer scale and recorded by Brodie bellows.

Stim. hypogastrics, coil 9 cm.: slight contraction, and then tension of bladder wall falls from 49 to 12 cm. while rhythm is abolished. As the lever writes on an arc of great curvature, at the top of the tracing it is much to the left of the vertical line through the signal.

Any rhythm that may have been seen before is checked. Generally the bladder recovers soon after the stimulus has ceased, doing so in my experiments no doubt with abnormal haste because the entering water was cool: but prolonged stimulation may cause such flaccidity that the bladder never regains its tone, not even after effective stimulation of the pelvic nerves. The initial contraction is of the muscle placed dorsally about the base of the bladder, and whether the bladder be in high or low tone, whether it be succeeded by inhibition or not, does not expel more than 8 c.c.; but when the bladder is empty, it seems to include a wider area and extend well above the entrance of the ureters. Relaxation concerns all the rest of the bladder and appears with a latent period of very few seconds[1]. The motor effect is always seen, but despite every

[1] Fagge (This *Journal*, XXVIII. p. 308. 1902) suggested that the inhibition described

precaution a full relaxation cannot in every case be demonstrated. Often at the commencement of the experiment the physiological tension of the bladder is very low, having perhaps been reduced to this level reflexly in the first stage of anæsthetisation[1]. Or it may be exceedingly high with a deep rhythm that almost defies inhibitor influence. If the pelvic nerves be cut to reduce this, the tension usually falls to the other extreme limit; and a like atonia may result when the brain is destroyed to avoid the need of anæsthetics. Yet in nearly all cases a little relaxation may be revealed.

Artificially raising the tone by slight exposure, or by the use of such drugs as caffeine or eserine, does not make it easier of demonstration. There is, however, one condition under which I find that the fullest relaxation may be shown again and again as the result of hypogastric stimulation. This is attained by degenerative section of one pelvic nerve. Three days after such a lesion the bladder is in fair tone and responds with great sensitiveness to the hypogastric nerves (cp. p. 419). As the change developes so early, it cannot be ascribed to the formation of new nervous ties, and indeed the response obtained does not differ except in its greater certainty from what may be observed in the normal cat.

Cell relays. The motor and the inhibitor nerves in the hypogastrics are, as described above, distinct from one another in their final area of distribution. Stewart (*loc. cit.* supra) claimed that a sharp separation can also be made between them in the nerve trunk, insomuch as the cell relays of the motor nerves are situated in the inferior mesenteric ganglia, but those of the inhibitors in the plexuses about the bladder itself. His analysis was made by Langley's nicotine method. This view I at first accepted; and it had the recommendation of providing a function for some of the odd 550 medullated preganglionic fibres identified by Langley and Anderson[2] in each hypogastric. In my earlier experiments stimulation of the inferior splanchnics, after the inferior mesenteric ganglia had been painted with ·5 % nicotine, caused a pure relaxation with a latent period of a few seconds: the

by Langley (This *Journal*, XXVII. p. 252. 1901), inasmuch as it did not develope until after the lapse of a minute, was not a direct effect but rather an after result of the first contraction. This cannot be accepted. The inhibition as a rule synchronises with the period of stimulation.

[1] To avoid such emotional changes I have narcotised animals with urethane alone. The cats never manifested annoyance, and passed purring into a state of unconsciousness. Yet the bladder was found to be atonic and useless for the study of inhibition.

[2] This *Journal*, XVII. p. 179. 1894.

hypogastrics gave both contraction and relaxation, but after the injection of 15 mgm. nicotine only contraction. These were experiments in which the voluminal changes were not extensive, and indeed the pure fall obtained by stimulation of the nerves above the ganglia, when the latter had been painted with nicotine, was of only 4 to 5 c.c. After the general injection of nicotine the tone of the bladder was altered, and then even that small relaxation was no longer in evidence. Apparently Stewart also was dealing with small movements, for the only curve reproduced in his paper (Fig. 1, p. 2) illustrates a relaxation that is little more than the inverted image of the initial contraction.

The difficulty lies in finding a bladder of which the physiological tension is not seriously altered by the injection of nicotine. As stated above, this quest is achieved by section, three to five days previously, of one pelvic nerve. In every such experiment stimulation of the hypogastrics was found to evoke inhibition as well as contraction of almost the same extent after as that seen before the injection of nicotine (cp. Fig. 14). Painting the inf. mes. ganglia with nicotine often excites fair inhibition; and then stimulation of the inferior splanchnics may cause in some animals contraction, in some a little relaxation, or in others a double effect. Clearly the main mass of the relay cells is that of the inferior mesenteric ganglia. There is no cleavage here of motor from inhibitor nerves[1], just as in the cœliac ganglia Langley proved there to be none of the vaso-constrictors from the intestinal inhibitors[2]. The analysis by nicotine is confirmed by the results of degeneration. Six or twelve days after section of the inferior splanchnics (cp. p. 413) the hypogastrics are still competent to produce inhibition of the body as well as contraction of the base of the bladder.

But a few relay cells for both nerves may at times lie more peripherally. The occurrence of such was postulated by Langley and Anderson[3] in their analysis of the "Sokownin reflex" from the inf. mes. ganglia as being one in preganglionic motor axons to such cells.

This reflex is observed immediately after section of the inferior

[1] Together with this error is removed the doubt whether adrenalin can inhibit plain muscle that has been deprived of its inhibitor nerves (This *Journal*, XXXII. p. 441. 1905). If a few inhibitor cells had chanced to be lying peripherally, these could hardly in ten days have acquired new influence over the rest of the muscle so as to render it all accessible to the action of adrenalin.

[2] Compare too the general rule given by Langley (This *Journal*, XX. p. 246. 1896: and *Ergebnisse der Physiol.* p. 840. 1903) that "each sympathetic ganglion is, broadly speaking, a cell station for all classes of visceral fibres which supply a definite area."

[3] This *Journal*, XVI. p. 415. 1894.

splanchnics, that is of the nerves uniting the inferior mesenteric ganglia to the C.N.S. Excitation of the central end of one cut hypogastric then evokes a slight contraction of the base of the bladder by impulses passing down the other hypogastric. All instances of such axon reflexes studied by Langley and Anderson in any tissue are of a motor type producing only contraction. Stewart[1] too observed only contraction of the cat's bladder by central excitation of one hypogastric.

In the normal bladder I was never able to demonstrate any inhibition as part of this reflex. To facilitate inhibition three experiments were made after degenerative section of the right pelvic nerve. Two of these gave only contraction as the "reflex": the third exhibited unquestionable inhibition. In it stimulation of the central end of the cut left hypogastric produced a contraction of 3 c.c. and relaxation of 10 c.c. on 35 c.c., while the right hypogastric excited directly gave the same contraction and relaxation of 30 c.c. But when the left hypogastric was teased it was found to contain a cluster of ganglion cells that had been split off the main mass and lay embedded in the trunk of the nerve only a few millimetres from the point of excitation. It was therefore possible that the exciting current had spread upward and directly stimulated the preganglionic nerves above these ganglion cells. So while the experiment showed that inhibition might be carried by a branching of preganglionic inhibitor nerves, just as is believed to occur with the motor nerves, it did not prove beyond doubt that any of the inhibitor ganglion cells lay quite peripherally. On Stewart's view that all the inhibitor ganglion cells lie peripherally, such axon reflexes of inhibition should be more in evidence than those of contraction, unless it be either that the inhibitor preganglionic axons do not branch down each hypogastric (a hypothesis disproved by the experiment just described) or that the inhibitor preganglionic axons of one hypogastric emit side branches to the ganglion cells of the contralateral motor axons[2].

However, though the nature of the mechanism concerned in the "reflex" may not be clear, there is less doubt about the main point required for the present discussion. Inhibition in addition to, though not so readily as, contraction can be caused in the "Sokownin reflex."

[1] *American Journal Physiol.* II. p. 182. 1899.

[2] The explanation of even the "reflex" contraction as a simple preganglionic axon reflex is not quite satisfactory. It may be that the phenomenon is conditioned by the presence of inhibitor as well as motor nerves in the trunk to the viscera in question.

The conclusion from this and from the other evidence regarding the position of the ganglion relay cells is that there is no distinction between motor and inhibitor nerves in the hypogastrics beyond that of their final area of distribution. These points may be considered in more detail.

In the first place it should be remarked that the area in which contraction is observed varies widely and, it would seem, aimlessly in different cats. It is always confined, as in the rabbit where the contraction is more uniform, to the dorsal surface of the bladder—generally to the little space between and adjacent to the ureters: but it may spread far beyond this almost to the apex of the bladder, and is in no wise restricted to the morphological area known as the trigone. The contraction is seen as a superficial crinkling and soon gives way to relaxation in the same area. Though the area in which the contraction occurs varies from individual to individual, it is constant during the course of an experiment[1] on any particular cat.

Adrenalin, whether injected intravenously or painted directly on the muscle, never causes any effect other than that of relaxation throughout the cat's bladder. Even on the trigonal area it causes relaxation[2], and thereby partly lessens the motor effect of stimulating the hypogastrics during its period of action.

An explanation of the motor action and of its incongruence with the response to adrenalin might perhaps be suggested by observations described later in this paper (p. 426), in which it appears that after section of both pelvic nerves the hypogastrics may develope an exaggerated motor control of the bladder, seemingly by uniting with the isolated pelvic ganglion cells. There might be a native tendency to this perverse union, which would always be sought by a few vagrant sympathetic fibres. The contraction would then fall altogether outside of the sympathetic class, and naturally not be simulated by adrenalin.

[1] Nor in a few experiments made two years ago was its extent altered by the injection of strychnine. In regard of the recent work of Sherrington and of Bayliss on the alteration of central reflexes by poisons these experiments need repetition.

[2] In an earlier paper (This *Journal*, XXXII. p. 404. 1905) I made the false suggestion that adrenalin causes contraction simultaneously with inhibition in the cat's bladder, and that the greater extent of the latter swallows up the small contraction. But even with a bladder which was so relaxed as to be incapable of further inhibition, though contracting by 4 or 5 c.c. in response to electrical excitation of the hypogastrics, adrenalin could evoke no demonstrable contraction. And if the upper four-fifths of the bladder be ligatured off and a record taken of volume changes in only the small bag formed by the base, adrenalin still causes only relaxation.

But that is not the nature and explanation of the hypogastric contraction, for the movement is not paralysed by the injection of nicotine; and it is slowly extinguished by ergotoxine[1]. It must therefore be recognised as being biochemically a true sympathetic contraction. The issue is now limited to two alternatives.

Either (*a*) the contracting muscle is a thin sheet spreading from the urethra over a variable surface of the bladder. It will be proved later that the urethral muscle is caused to contract by the hypogastrics and also by adrenalin.

Or (*b*) the initial contraction is an error, an abnormal response due to the unnatural stimulation of the hypogastrics, and would never occur in the functional use of the bladder.

This latter assumption (*b*) would agree fairly with the inability of adrenalin to cause contraction, for it seems that the resemblance between stimulation by this drug and by the sympathetic nerves respectively is closest where functional use of the nerves is most frequent[2]. It would also serve well to explain the abnormally innervated bladders of two cats in which the motor as well as the inhibitor action of the hypogastrics was in abeyance.

Still this view is rendered almost untenable by the fact that the constriction does not play irregularly over the surface of a bladder, but is restricted always to a definite area in each individual. Such uniformity rather indicates that the difference must be referred by (*a*) to a separate morphogenesis of the tissues innervated by the motors and inhibitors respectively. A comparison of the bladders of different mammals favours this view. Such a separate sheet of muscle would be distinct from that which is thrown into contraction by the pelvics and inhibited by the hypogastrics, and its contraction would—as is indeed the case—always be apparent as an added effect when the hypogastrics are excited during maximal contraction by the pelvics.

Abnormalities in the hypogastric innervation. A summary is given of the examination of the two cats in which, a rare abnormality, the hypogastrics seemed to have missed union with the bladder.

Large ♂. Ether. Bladder was in high tone, the pelvics being uncut. Stimulation of the hypogastrics had no effect on it, though the vasa deferentia contracted well. Intravenous injection of adrenalin, 0·3 mgm., did not lessen the rhythm and indeed evoked a sharp contraction: this contraction was simply due to stimulation of the spinal centres of the pelvic nerves, for when the pelvics were cut and the bladder tone fell, adrenalin produced in it no change at all. Then too stimulation of the hypogastrics was followed

[1] Dale. This *Journal*, xxxiv. p. 184. 1906.
[2] Elliott. This *Journal*, xxxii. p. 416. 1905.

by an exceedingly small contraction of the urethral end of the bladder. The usual stout branches ran from the inferior mesenteric ganglia with the artery to the colon: but the hypogastrics were very slender, and, while taking the normal course past the ureters to the vasa deferentia (in which they did cause contraction), did not supply the branches directly to the vesical plexus that in the normal cat are so evident. Apparently the sympathetic vesical fibres were absent, and consequently no volume changes were caused by adrenalin.

Large ♀. A.C.E. The bladder was in fairly high tone from which it fell later when the sacral nerves were cut. Excitation of the hypogastrics caused no detectable change in it. The injection of adrenalin, up to 0·6 mgm., did not relax the bladder even when it was in high tone; nor did a like amount lessen the power of the pelvics to cause contraction. The pelvics were very sensitive to excitation. The experiment was not done under quite satisfactory conditions, insomuch as A.C.E. was employed as anæsthetic and was twice given in excess so that the cat was with difficulty kept alive. But the functional lack of connection between the hypogastrics and the bladder agreed with the results of dissection. For this, the viscera were fixed with 1 °/₀ osmic acid. The usual branches were given off by the hypogastrics to the colon and urethra: none ran up to the plexus on the wall of the bladder. Dissection included the inferior splanchnics, so that error by loss of an accessory hypogastric was excluded.

Though neither of these cases was analysed exhaustively, the results were sufficient to indicate the absence of the usual sympathetic nerves to the bladder. No third such example has occurred with me. On the bare chance of the abnormality being found as an associated defect, I tried a blue eyed albino ♀ cat, which as usual was deaf: but the innervation of its bladder was typically normal, and indeed provided the curve reproduced (Fig. 1) to illustrate hypogastric inhibition.

Two points in the behaviour of the abnormal bladder deserve emphasis. First that adrenalin was as incapable as the hypogastrics of relaxing the bladder, though the muscle was in all other respects of normal character as regards rhythm, reaction to the pelvics, etc. Secondly that the motor fibres as well as the inhibitors of the hypogastrics were lacking.

Pelvic visceral nerves.

On the integrity of these nerves depends the tone of the bladder in the cat. Section of them causes immediately its relaxation, and that without even a contraction by the stimulus of the cut. Rhythmic movements, if present, cease at the same time. Later a rhythm may develope and the tone in part return. Exposure of the bladder, and especially the injection of nicotine, promotes such rhythm. This result of exposure makes it of course impossible to observe clearly the loss of tone by cutting the nerves, unless they are dissected out above the rectum without opening the abdomen or exposing the bladder. Gentle stimulation of the nerves induces at first a rhythm: as the stimulus increases the bladder contracts slightly, and the rhythm deepens on the higher base line. Stronger stimulation elicits a rapid contraction of such power as to raise the intravesical pressure to more than 60 cm. of water.

Both by degeneration and by nicotine were confirmed the observations of Langley and Anderson[1] that the cell relays of these nerves are in the ganglia on the wall of the bladder. Even at the height of the pelvic contraction the hypogastrics can still produce their usual motor effect. Probably therefore the muscle concerned in this last movement does not receive motor nerves from the sacrals.

The antagonism between the pelvic motors and the sympathetic inhibitors is as that described elsewhere[2] for the first nerves and adrenalin. The motor impulses are generally dominant over the call to inhibition; but when the inhibitor nerves are stimulated strongly and the motors weakly, the contraction due to the latter is greatly lessened. The inhibition induced by the hypogastrics seems to be of precisely the same character as that caused by adrenalin. With reference to its ultimate bearing on the muscle, there needs to be explained an earlier statement of mine (*loc. cit.* p. 455) that "such inhibition can check an isotonic contraction by the pelvics more readily than it can an isometric development of tensile stress without shortening." It had then seemed to me that the processes of inhibition impeded the shortening of the muscle fibre rather than its tensile pull. The differentiation, however, rested on imperfect analysis. Large quantities of adrenalin, for example 0·6 mgm. intravenously, could arrest an isometric contraction as well as the isotonic. Still, with moderate excitation of the pelvics adrenalin did undoubtedly hinder contraction much more than the pressure rise. In these experiments the bladder was at the start placed under the same conditions of pressure and volume, p and v, for each mode of registration. But the injection of adrenalin under constant pressure conditions enlarged the bladder to p, $v + v'$, so that its radius of curvature and muscular tension ($T \propto P \, . \, V$) were greater and the sheet of muscle therefore less apt for contraction by the pelvics. On the other hand with constant volume the injection of adrenalin relaxed the bladder to $p - p'$, v, its radius of curvature remaining unaltered and its muscular tension being actually lessened: it was therefore better prepared for activity than it had been before.

This contrast in physical conditions was enough to explain the differing results. Under either set of conditions the physiological result of the inhibition was to oppose the impulse to contraction by the pelvic nerves.

[1] This *Journal*, xix. p. 377. 1896.
[2] Elliott. This *Journal*, xxxii. p. 455. 1905.

The Urethra.

The urethra of the cat is admirably adapted for experimental study. It stretches as a uniform tube of plain muscle with a length of rather less than 4 cm. from the pyriform bladder to the prostate gland or the upper edge of the symphysis. Its mobility and the large size of the bladder, which on this long stalk can slip easily into any position among the viscera, are a special development whereby the cat can store relatively greater quantities of urine than other animals.

Regarding its innervation there is only the statement of Langley and Anderson[1] that the "hypogastrics have little if any effect on the urethra." Stewart[2] believed that the sacrals carry motor impulses to it, their tonic influence being centrally inhibited by central excitation of the sciatic or the hypogastrics.

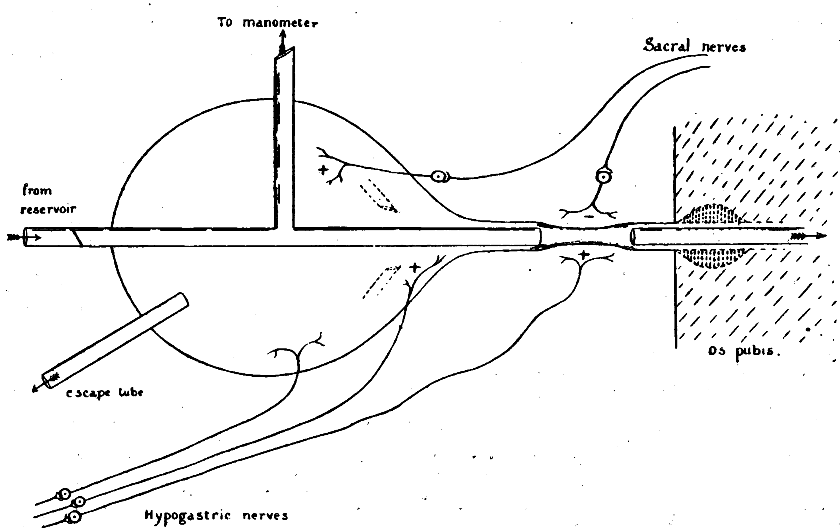


Fig. 3. Diagram of apparatus for measuring resistance of cat's urethra. Description in text.

Mere watching with the eye is insufficient to discover the muscular movement; and the inner diameter of the tube is too small for the insertion of a balloon recorder. Trustworthy evidence can best be obtained by measuring the pressures under which an entering fluid wedge just overcomes and is in turn overcome by the resistance of the urethral muscle. The method is explained by the diagram Fig. 3. The

[1] This *Journal*, XIX. p. 73. 1895.
[2] *American Journ. Physiol.* III. p. 5. 1899.

apex of the bladder was opened, and a cork tied in by a ligature more than halfway down its wall. Through the cork passed an open short tube communicating with the interior of the bladder, and a longer one which was pushed down into the urethra for any desired distance. This latter was fed through a valve with salt solution at 38° C. from a reservoir placed at some height. By a side tube the water on the urethral side of the valve was connected with a water manometer on which the pressure was directly read, while a continuous record of its changes was also inscribed by a bellows recorder. A second tube was passed up the urethra from below, and lay with its open mouth at any desired distance below that of the upper.

Change of intravesical pressure simply drove water out of the side escape tube without affecting the head of pressure in the upper urethral tube. When the valve was opened (as indicated by the sign + in the tracings reproduced), water slowly entered from the reservoir till the rising pressure forced the resistance of the urethra between the tubes and water escaped by the lower, its exit being registered by a tambour drop recorder. So soon as this occurred, the influx of water from the reservoir was stayed, and the pressure at which the urethra resisted passage in turn observed. With so long a urethra a strip could be studied 2 or 3 cm. below the bladder, where it was far beyond the range of effect of any pull of the vesical muscle. It was very necessary to keep the upper and lower tubes centred on the same axis and an invariable distance apart, so as not to alter the longitudinal tension on the urethra. In some experiments this was effected by clamping the upper and the lower apparatus firmly, though separately, to the table: in others by the use of brass tubes to which were soldered three lateral stays binding all into a rigid system.

Often the urethra was never exposed, and the position of the tubes was ascertained by feeling with the fingers. But for a short experiment both contraction and inhibition can be well enough demonstrated in a urethra that has been exposed, raised up in air from the neighbouring viscera, and covered only with a light moist flannel.

Stimulation of the hypogastrics produced immediately constriction of such power that 1 cm. of urethra could uphold a pressure of from 50 to 60 cm. of water (cp. Fig. 4). The resistance yielded as soon as excitation ceased, and the subsequent flow of water through caused a passive dilation of the tube so that its closing pressure was for a time a little lower than before the contraction. The response is not easily fatigued by repetition of the stimulus. A tracing (Fig. 5) is given in illustration of the similar effect of adrenalin when injected into the jugular vein. The contraction is then prolonged a little later than that of the blood vessels, and the relaxation is discontinuous. It is only in the male that the urethra possesses a sheet of muscle with such powerful innervation, where unyielding constriction is needed to prevent regurgitation into the bladder from below the prostate, when the secretion of the testicles is driven forcibly through the lower urethra against the resistance of the surrounding erectile tissue. The urethra

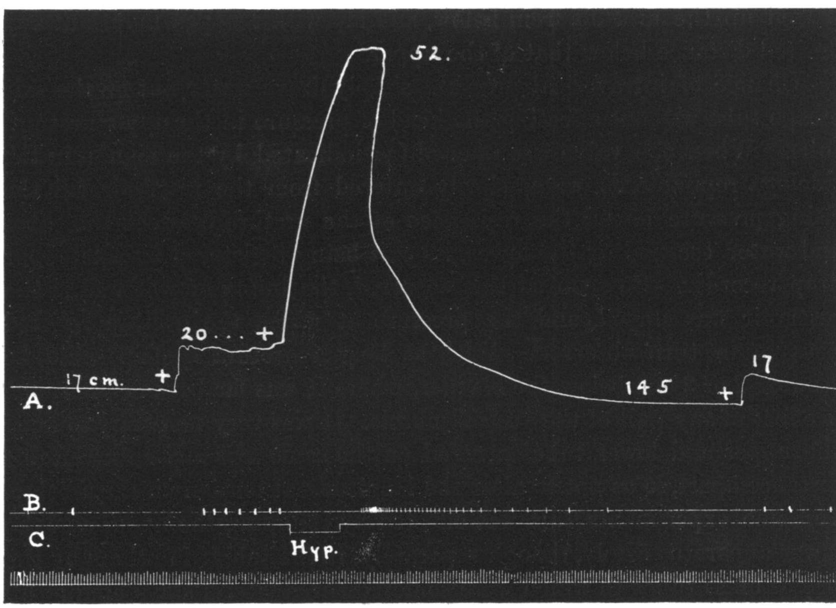


Fig. 4. Constriction of the cat's urethra by the hypogastric nerves. Ether: pelvic visceral, and hypogastric nerves cut. Tubes were introduced into the urethra from the bladder and from below the prostate gland, so that their orifices lay about 2 cm. apart, being separated by that length of closed urethra. Salt solution at 38° C. was driven into the upper tube at a pressure which could be varied at will. The head of pressure was recorded in centimetres of water by a manometer, and graphically traced by a bellows recorder, line *A*. When the fluid forced open the urethra, it escaped down the lower glass tube and its dropping outflow was recorded by a bellows recorder, line *B*. *C* is the signal. Time marked in seconds.

The urethra just closes against 17 cm. water. Under a constant pressure of 20 cm. a slow flow through it is maintained. Then both hypogastrics are stimulated. The resistance is raised thereby and does not yield to a pressure of 52 cm. When stimulation ceases, the urethra relaxes and opens again as before at 17 cm.

The rise of the lever in line *A* to 52 cm. marks an artificial (+) increase of pressure and is in no way caused by the constriction of the urethra.

in the female cat could not withstand a pressure of more than 35 cm. Section of the hypogastrics in my experiments did not at once lower the resistance of the urethra[1].

These motor sympathetic nerves pass directly from the hypogastric plexus to the urethra at all points: a ligature placed around the urethra and upper tube at successive levels below the bladder does not abolish their power, nor does one around the lower tube above the prostate. By moving the system of tubes it appears that there exists no special sphincter area, for a contraction of equal power is exhibited at any point in the urethra. Just below the prostate a similar contraction occurs: further I did not investigate because the urethra is complicated by the addition of striped musculature.

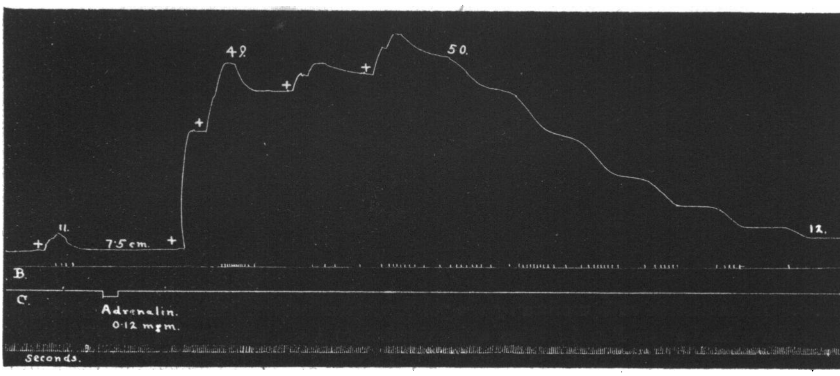


Fig. 5. Constriction of cat's urethra by adrenalin. Same arrangements as in experiment of Fig. 4. Muscle of urethra fatigued, as its nerves had already been stimulated at intervals for 2 hours. It opens under pressure of 11 cm. and closes at 7·5 cm.

Inject 0·12 mgm. adrenalin into ext. jug. vein. Urethra resists to 49 cm. and then to more than 50 cm. Afterward it gradually relaxes to a resistance of 12 cm. The sign + indicates artificial increase of fluid pressure. Time marked in seconds.

The cell relays for these motor nerves are shown by the action of nicotine to lie almost all in the inferior mesenteric ganglia. I have never observed on the urethra a motor axon reflex like that described by Sokownin for the bladder. This would agree with the anatomical fact stated by Langley and Anderson[2] that no medullated (and therefore probably no preganglionic) nerves pass from the sympathetic to the urethra. Many medullated nerves were observed by them to reach the

[1] Contrast this with the dependence of the internal anal sphincter on the hypogastrics, Langley and Anderson. This *Journal*, XVIII. p. 83. 1895.

[2] This *Journal*, XIX. p. 378. 1896.

urethra from the sacral nerves. Of these a large proportion would be sensory; but doubtless some were preganglionic fibres carrying sacral inhibitor impulses.

To show such inhibition it is essential that the pelvic nerves be dissected out above the rectum where injury to the pelvic plexus cannot be done. The relaxation develops rather slowly, and it does not lower the resistance by more than a few centimetres (cp. Fig. 6). But its occurrence may be proved again and again in the same animal, or otherwise illustrated by the acceleration of a slow flow under constant pressure (cp. Fig. 7) when the pelvics[1] are excited.

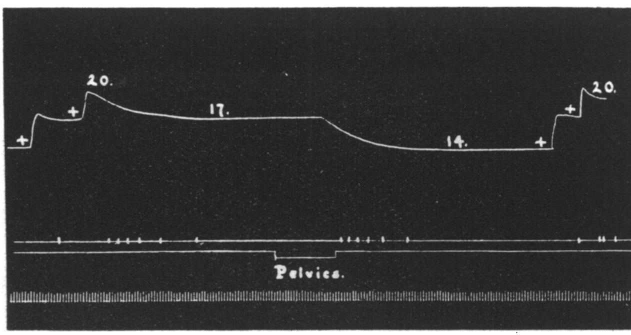


Fig. 6. Relaxation of cat's urethra by the pelvic visceral nerves. Same arrangement and same animal as in Fig. 5 : tubes approximated to 1 cm. and urethra lying exposed, but under a warm sponge. It opens at 20, closes at 17 cm. Stim. both pelvics above rectum, coil 9·5 cm. ; no escape of current to other muscles ; urethra relaxes, closing at 14 cm. Subsequently opens again at 20 as before.

The appearance of the urethra in the diagram might suggest that such opening was only the result of its being straightened by an active contraction of the outer longitudinal coat, a coat that is histologically well developed and contains quite as much muscle as the inner circular. Before this explanation there are obvious difficulties. Even supposing such contraction mechanically capable of widening the passage, its result, the opening, should occur with less delay than was actually observed. Moreover the method would be a physiological oddity, an unsatisfactory means to an end which could be better attained by simple inhibition.

[1] In two experiments the pelvic nerves chanced to produce contraction of the urethra up to 40 cm. water, and thereafter the hypogastrics were rendered ineffective for two or three minutes: but both before and after this peculiar result the pelvics caused normal inhibition in the same animals.

However, twelve experiments were made to examine the question by direct measurement of the changes in the length of the urethra. For this purpose the bladder was opened freely, and the urethra transected a little above the level of the symphysis. A thread attached to this cut end allowed it to be extended by a direct weight of 5 or occasionally 10 gm., and, being connected with a lever, recorded with ninefold magnification the shortening or lengthening of the muscle. The upper end of the urethra below the bladder was fixed by impaling it upon a fork made of three needles soldered to a metal rod that was

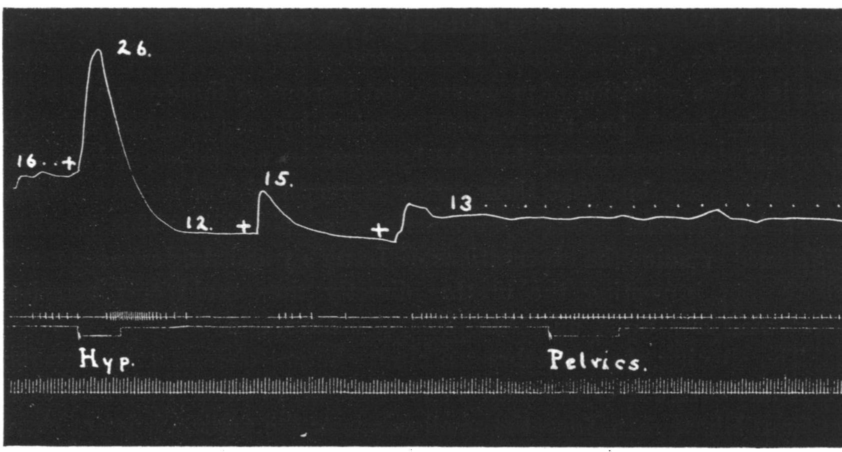


Fig. 7. **Acceleration of flow through cat's urethra caused by excitation of pelvic visceral nerves. Apparatus as before: nerves from spinal cord cut. Urethra opens at 16 cm. permitting slow flow through. Stim. hypogastrics, coil 10 cm.: urethra resists to 26 cm. (♀ cat): opens again at 15 cm. Then slow flow through, under 13 cm., is accelerated by stimulation of the pelvic nerves, coil 10 cm.**

clamped to the table. By this means the nerves and blood vessels passing down from the bladder were not greatly injured; and the fixed point being nearest to the bladder, any pull transmitted to the urethra from a contraction of the bladder above would simulate contraction and not inhibition of the urethra. When the urethra was transfixed 3 or 4 mm. below the bladder, no such transmitted pull vitiated the record from the available 15 to 20 mm. below.

The enveloping fat was removed, and the urethra raised well above the underlying viscera. Excitation of the pelvic visceral nerves always caused some relaxation, the length being increased at the most by one-twentieth. In both axes of the tube, then, these nerves cause the muscle to relax, and their action must be simply inhibitor.

But the hypogastrics do not innervate equally the circular and the longitudinal muscles; for the urethra shortened but a very little in response either to their excitation or to the injection of adrenalin, although in every case the lower part of the empty bladder was seen to contract very actively with each stimulation of the hypogastrics. In one experiment, however, manifest shortening of the urethra by one-seventh of its length followed stimulation of the hypogastrics or the injection of adrenalin. The cat in question was a female far gone in pregnancy, and the urethra was involved with the overgrowth of the uterine muscle; but the contraction was undoubtedly its own, for it was seen that the same nervous stimulation caused the underlying cervix uteri to relax. Three further experiments were consequently made on cats in a like condition of pregnancy, but in none of these was a greater shortening found than that normally produced in non-pregnant animals. It would therefore appear that the hypogastrics are motor to both the muscular coats, but that their action is very slight in the case of the outer longitudinal though its muscle is so plentiful. This peculiar difference explains the observations of Langley and Anderson quoted above; for inspecting the urethra directly they could only perceive shortening and must miss the internal constriction.

The opening of the urethra can always be provoked as a reflex under ether and curare from the central end of the great sciatic nerve, but not, so far as I have seen, from the small sciatic or the pudic. It is not clear why the one nerve should, and the other should not, be capable of easily influencing the sacral visceral cells in the cord. The two ineffective nerves, the pudic and lesser sciatic, are nearer segmental relations of these cells than is the great sciatic. Perhaps the association is that of habitual attitude.

Micturition.

Reflex evacuation of the bladder is easily produced by its over distension in the etherised cat. The reflex is unaffected by section of the hypogastric nerves, but disappears when the pelvics are cut[1]; and it fails when the C.N.S. is depressed by any shock, for example often by that of destroying the brain.

Goltz[2] described a scheme by which the conscious reflex for micturition could arise. Growing distension of the bladder was to increase the amplitude of its rhythmic movements, until on the crest of

[1] Cp. Guyon, on curarised dogs, *Comptes rendus Soc. de Biol.* p. 712. 1900.

[2] *Pflüger's Archiv*, VIII. p. 478. 1874.

one of these a few drops of water were forced past the barrier of the sphincter into the urethra, and stimulating its mucous membrane caused the "harndrang." Reflex contraction of the bladder was indeed recognised by Goltz to be a natural reaction to its distension: subsequent to this came the affection of consciousness by the irritation of the urethra, and then deliberate facilitation of discharge, or its repression, by willed contraction of the abdominal muscles or of the sphincter respectively. His view has been accepted by many writers, but a little distorted into the belief that the whole reflex originates from the urethra. That is opposed alike to clinical observation and physiological experiment[1]. The reflex is not lost in cases, as that of gonorrheal urethritis posterior, where the mucous membrane of the urethra is destroyed: it can be perfectly well produced in the cat when a catheter lies occluding all the urethra and with a ligature tied around it close to the neck of the bladder.

Obviously the reflex is determined, as Zeissl and Guyon maintain, by the tension of the bladder muscle. The actual tension of the wall varies directly as the product of the volume of fluid contained and of the pressure to which it is submitted; consequently it is impossible to name a critical value of either pressure or volume independently as determinant of the reflex. Mosso[2] indeed found that a trained and unanæsthetised dog exhibited the reflex always at a constant pressure of 20 cm. whether the volume were of 60 or 120 c.c., and he concluded that the fluid pressure is the essential factor. But I have produced it repeatedly at quite low pressures by simple increase of volume. In one Exp. under A.C.E. the pressure values as the volume was raised were v. 10 c.c., p. 0·5 cm.; 20 c.c., 2·0 cm.; 30, 2·0; 40, 2·5; 50, 4·0; then oscillatory rise to 60 cm., at which level, being the top of the manometer, 40 c.c. were discharged: again v. 20 c.c., p. 2·0 cm.; 40, 3·0; and rise to discharge 30 c.c. at 60 cm. In another cat the reflex was obtained at a pressure of 8 cm. with any volume above 40 c.c. But a third bladder, that had been chilled by exposure, would not tolerate more than 15 c.c.

[1] The old explanation is refuted too by an experiment of Müller (*Dtsch. Ztsch. f. Nervenheilkunde*, XXI. p. 130. 1901). A dog's spinal cord was transected at about Th. 13, thus leaving all the bladder nerves intact. Reflex evacuation subsequently developed to full power. Yet often, as the animal moved about, water was observed to trickle out from the urethra without causing a reflex discharge. Fluid in the urethra did provoke a reflex contraction of the ischio- and bulbo-cavernosus. The discharge from the bladder was not altered when the lumbo-sacral cord was then excised from about L4 to the upper end of S1.

[2] *Archives Ital. de Biol.* I. pp. 97 and 291. 1882.

Obviously, however, simple increase of muscular tension by voluminal dilation is not the single originator of the reflex, for not even in the most civilised beings, where central dominance of the reflex is greatest, is there apperception of the volume of the vesical contents.

The reflex may be influenced from various points. Thus in one case the bladder was filled by successive steps of 10 c.c. up to 60 c.c., the pressure then remaining steady at 12 cm. Rhythmic compression of a nipple—the cat having recently suckled kittens—now caused the tension to rise a little and the bladder then contracted fully. The experiment was repeated, with the same atonia on distension and the same facilitation of the reflex by touching the nipple.

Origin in the spinal cord of the pelvic visceral nerves. The nerves to the cat's bladder issue by the 3rd, 4th, and 5th lumbar, and by the 2nd and 3rd sacral spinal roots. There is no proof that efferent nerves issuing by any spinal roots may arise from cells at a remote segmental level and travel some distance in the cord before emergence. Yet that view is suggested by some work touching the position of the vesical centres. For example Stewart[1] showed that motor impulses from the brain to the cat's bladder cross in the cord as low as L5, but that reflex contraction from the great sciatic failed after transection below L2. So he agreed with his predecessors that the vesical centre lay at L4, making the more or less implicit assumption that the spinal cells for the sacrals had the same station.

The micturition centre is undoubtedly lower. Müller (*loc. cit.* p. 131) observed complete discharge in a dog whose lumbar cord had been excised down approximately to the first sacral. I noticed forcible spontaneous evacuation in cats five days after transection of the cord below L6. It was a good reflex contraction, and quite unlike the abnormal compensatory movements developed later after injury of the proper sacral machinery. To ascertain precisely whether or no a few sacral efferent nerves do travel down the cord I made use, at the suggestion of Professor Langley, of the method of degenerative section followed by histological analysis.

In four experiments the spinal cord was completely transected. Intervals of 5 to 8 days were allowed for degeneration of the motor nerves. One transection was just above[2] L5, the great sciatic arising from L6 and L7; and two were just above L6, the origin of the sciatic

[1] *American Journ. Physiol.* II. p. 182. 1899, with full references to previous work on this point.

[2] The fifth lumbar being the sixth subcostal nerve.

being the same. In none of these was a single degenerated fibre revealed by osmic acid in either pelvic visceral nerve. The fourth transection was between L7 and S1. On the right side, where the pelvic was derived chiefly from the first sacral, about half the fibres were degenerated; on the left, in which the second sacral was the chief source of these nerves, only one-third showed the injury. Excluding the sensory nerves, maximum degeneration of all the efferent fibres would have affected about two-thirds of the trunk. The close approximation of the spinal segments below L7 made it difficult to cut the cord at one without traumatic injury of the next lower. So the analysis was not made in greater detail. But the anatomical facts agreed with the deduction from the physiological reflex. Not a single motor cell of the pelvic nerve is situated above the spinal root origin of the great sciatic nerve.

An attempt was made to determine the position of these cells by Nissl's chromatolysis. In the experiments the right pelvic nerve was cut dorsally of the rectum by incision at the root of the tail. My operation involved the injury of very few other nerves, at the most of a few motor fibres to the caudal edge of levator ani; for the skin cut was only a matter of sensory nerves, and the recto-coccygeus is itself innervated by the pelvic postganglionic fibres. After 5 to 15 days the cat was examined under ether, killed, and its vessels washed out with warm saline and then with fixing fluid. The spinal cord was then removed into absolute alcohol, or in other cases it was directly excised without preliminary fixation and hardened in alcohol.

Many serial sections were prepared, but the results were not quite conclusive. No alteration was observed in any cells of the great anterior horn. A group situated dorsally of these at the angle in the twixt horn region, and just internal to the white matter, always presented some change. As the cells were small, elongated, and possessed little cytoplasm, they could not be judged easily by change of the Nissl staining granules: but in thick sections their nuclei were seen to be displaced excentrically. Accepting, though with diffidence, this nuclear change as a token of the cells affected by section of the nerve, one would then believe the spinal cells of the sacral visceral nerves to have the same position[1], relative to the great mass innervating the striated muscles, as has been assigned to the correspondent cells of the thoracico-lumbar or sympathetic nerves.

[1] Cp. references in Herring's paper. This *Journal*, xxix. p. 282. 1903; also Bruce's survey of the intermedio-lateral tract in man, *Trans. Roy. Soc. Edinburgh*, 1906.

II. The Dog.

Most of the work on the bladder by continental physiologists in the last 25 years has dealt with the dog alone. The mass of observations so accumulated renders it unnecessary for the broad purpose of this paper to study the dog more closely. Only a few experiments were made to test the main results already described.

Hypogastric nerves. From Gianuzzi's observation in 1863, that a slight contraction of the bladder answered to impulses carried by these nerves, there was no advance until in 1893 Zeissl endeavoured to establish the validity of Von Basch's law in the bladder, to prove that the hypogastrics are motor to the circular muscle of its sphincter, inhibitor to its body. In a series of papers[1] and by varied experiments he sought to uphold such inhibition. Not one of his published curves illustrates the desired movement. The best (*Wiener Klinik*, p. 147. 1901) gives no quick clear downfall after the primary contraction: the relapse is slow, slight, and not other than might be ascribed to a passive yielding of the bulk of the bladder. The claim based upon these curves is not substantiated by any numerical measurements of pressure and volume changes. Griffiths[2] stated that occasionally a fall of pressure followed stimulation of the hypogastrics; and that such could be reflexly produced by central excitation of the pudic nerves. In the latter case he did not distinguish between central and peripheral inhibition. Since then the occurrence of inhibition has been denied by all workers. Rehfisch[3], Fagge[4], and Wlasow[5] agree that the sole response is that of a slight contraction.

I have made eleven experiments on this question. A pressure rise of 1 to 4 cm. water, or a voluminal contraction of 10 c.c. on a vol. of 150 c.c., or of 20 on 350 c.c., p. 15, resulted from excitation of the hypogastrics, but never a fall that having regard to the general trend of the tracing, could seriously be attributed to inhibition. Indeed the contraction was generally sustained. Especially was it so when the tension of the bladder

[1] *Pflüger's Archiv*, LIII. p. 560. 1893: LV. p. 569. 1894: LXXXIX. p. 605. 1902: *Wiener Med. Wochensch.* pp. 460 and 1202. 1901: and general summary in *Wiener Klinik*, XXVII. p. 125. 1901.

[2] *Journ. Anat. and Physiol.* XXIX. pp. 61 and 254. 1895.

[3] *Virchow's Archiv*, CLXI. p. 529. 1900.

[4] This *Journal*, XXVIII. p. 304. 1902.

[5] *Centralblatt f. Physiol.* p. 776. 1905, and reference in Hermann's *Jahresberichte*, XII. p. 75.

wall was already high by reason of great distension, that is precisely under those conditions which facilitate the demonstration of inhibition in the cat. The contraction is not extensive and it developes more slowly than in the cat; but it is powerful, for it can produce a further rise even when the intravesical pressure is greatly exalted by stimulation of the pelvics. The inferior splanchnics are generally more effective than the hypogastrics.

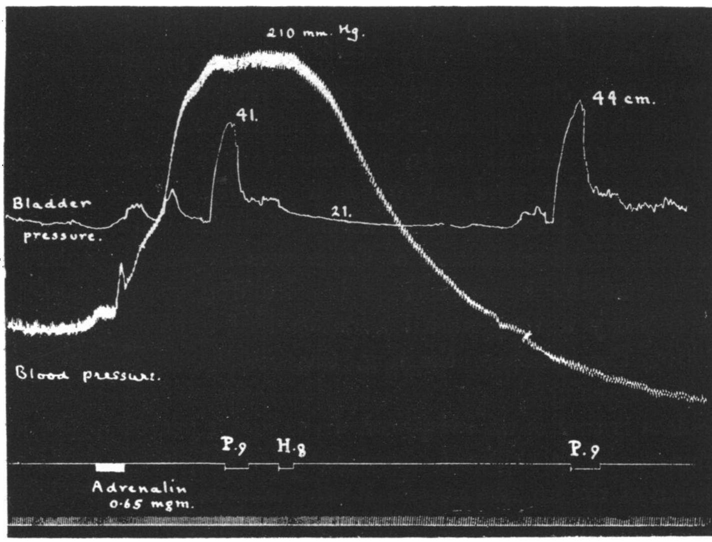


Fig. 8. Dog. A.C.E. Vagi cut; also hypogastric and pelvic nerves to bladder. Shielded electrodes on hypogastrics and right pelvic nerves. Catheter up urethra, and bladder pressure changes recorded with constant volume of 30 c.c.

Adrenalin, 0·65 mgm., injected. Slight contraction of the bladder resulted; but stimulation of the right pelvic nerve caused practically the same pressure rise both during and after the time of adrenalin action. P 9 (secondary coil at 9 cm.) and H 8 (secondary coil at 8 cm.) indicate stimulations of the one pelvic and of both hypogastric nerves respectively.

Anæsthetics were changed; unipolar stimulation and other means tried: but all failed to cause inhibition. Nor could I reproduce the fall described by Griffiths as a central reflex from the pudic nerve. This failure agrees with Zeissl's experiments, though not his theory. Moreover it is supported by the fact that adrenalin produces in the dog's bladder only a slight pressure rise, similar to that caused by the hypogastrics, which then temporarily lose their power of causing a rise while the action of the pelvics is not thereby suspended (cp. Fig. 8). Ergotoxine[1] has a curious effect. The drug in general paralyses contraction but not inhibition by the sympathetic nerves or by adrenalin. Thus in the cat it annuls the constriction of the urethra, but allows full relaxation of the bladder. In the dog it simply inverts the response to adrenalin. A bladder which with a vol. of 350 c.c., both pelvic and hypogastric nerves being cut, contracted 20 c.c. when the hypogastrics were excited, after the injection of ergotoxine relaxed to precisely the same extent in response to adrenalin: the hypogastrics then produced a diminished contraction. It is probable that a much larger dose of ergotoxine would have gone further, and not only paralysed the hypogastric contraction but have actually enabled these nerves to produce a slight relaxation similar to that caused by adrenalin after moderate doses of the poison. This was indeed proved to be the case in the ferret (p. 398), but parallel experiments were not made on the dog.

The evidence drawn from the action of drugs combines with that based on the direct excitation of the nerves to justify an unreserved statement that the hypogastrics in the dog supply functional nerves to only a very small area in the base of the bladder. Considering the habits of the dog, the absence of general inhibitor nerves is surprising.

The area is that of an outspread of the motor nerves to the urethra and sphincter of the bladder. Budge[2] observed that direct electrical stimulation of the urethra caused its contraction. By Zeissl (*loc. cit.* 1893 and 1894), Rehfisch[3], and Wlasow it was proved that outflow by the urethra is checked upon stimulation of the hypogastrics. Courtade and Guyon[4] gave direct records of the contraction of the muscle at the neck of the bladder, and Fagge illustrated the closure by balloon records from the interior of the urethra, while he determined its power to be such as would resist a head of 46 cm. water[5].

[1] This is the name now given by Dale to the active principle of ergot which is contained in the substance previously described by him as chrysotoxin (This *Journal*, XXXIV. p. 163. 1906).

[2] *Pflüger's Archiv*, VI. p. 306. 1872.

[3] *Virchow's Arch.* CLXI. p. 529. 1900. In a previous paper (*ibid.* CL. p. 111. 1897), Rehfisch tabulates numerous observations on the closing pressures of the sphincter in life and death, and also recapitulates many experiments on the action of the sphincter in man.

[4] *Arch. de Physiol. norm. et path.* p. 622. 1896.

[5] The few observations that I made on the dog did not reveal so powerful a constriction of the urethra. The sphincter at the neck of the bladder contracted fairly when the hypogastrics were stimulated, but the adjoining urethra, in the female at any rate, was not forcibly constricted (cp. Exp. p. 406). It is conceivable that the dog, with its habit of

Sacral or pelvic nerves. Their motor control of the bladder requires no discussion. Fagge measured the rise of intravesical pressure so caused, and found it to be 24 cm. of water, that is a little more than enough to overcome the normal resistance of the sphincter. The value is far too low. Narcotisation by morphia could not have been alone responsible for the apparent weakness; for in a small terrier that had received 80 mgm. of morphia and had been under A.C.E. for three hours I found the pelvic nerves to be capable of raising the intravesical pressure up to one and a half metres of water.

Rehfisch, Fagge, and Wlasow do not accept the view enunciated by Zeissl, that the sacrals relax the dog's sphincter. Believing that the hypogastrics constrict the orifice, the choice lies between three means for its dilation in micturition:

i. central inhibition of tonic contraction.

ii. passive dilation by the pull of the contracting bladder.

iii. active inhibition of the muscle itself.

The first is approved by Rehfisch, and advocated by Stewart for the cat though he is driven to suppose that the sacrals are the efferent path for urethral contraction. Zeissl's experiment of tying a large tube into the base of the bladder, when outflow without pressure rise resulted upon stimulation of the pelvics, placed beyond doubt a real dilation of the sphincter by these nerves. The reflex dilation from the central end of the great sciatic was also shown to depend on their integrity and not on that of the hypogastrics, so that it too was not a case of central inhibition of tone. But the dilation might be partly attributed to the action (ii) suggested by Kohlrausch and others, for the ligature around the base of the bladder would not check the contraction of the small portion of the detrusor extending from the ligature to the urethra. Hanc[1] made a fair differentiation between ii. and iii. by studying how various poisons could selectively affect the two responses. Under uniform conditions the reflex response to central excitation of the great sciatic varied widely in its relation between rise of intravesical pressure and urethral outflow. With strychnine at times outflow occurred earlier than the bladder contraction. These experiments are not quite conclusive, for they made no analysis of the efferent paths. Moreover changes in the character of contraction of the poisoned detrusor or an inversion of the nature of the C.N.S. reflexes might be responsible for the varying relations between

arrested micturition, has developed rather the power of instantly checking outflow by contraction of the striated muscles lower down the stream.

[1] *Pflüger's Arch.* LXXIII. p. 453. 1898.

pressure rise and outflow. Franklhochwart and Fröhlich's[1] results touch more nearly the point at issue. Employing Zeissl's method they observed that in 8 out of 21 dogs stimulation of the cortex cerebri produced outflow without pressure rise. The hypogastric nerves were cut, excluding central inhibition of impulses passing by these nerves.

Against this Fagge's observations do not weigh heavily. The slight contraction about a balloon recorder in the urethra noticed by him, when the pelvic nerves were stimulated, might have been due to dilation of erectile tissue. And the argument based on the fact that the opening pressure for outflow is the same whether it occur with pelvic excitation or artificial increase of intravesical pressure counts for little in view of the rapidity of the detrusor contraction and the longer latent period of sphincter relaxation under the abnormal conditions of experimental study: identity of the closing pressures would have been a more serious objection.

So the sum of the evidence is decidedly in favour of the simple and natural mechanism, that is of inhibition of the sphincter, similar to that occurring in the cat and, as will be seen later, in the rabbit.

III. The Rabbit.

The bladder is very thin walled and elongated, the entrance of the ureters being at a distance from the apex of less than half the bladder's total length. If the orifices of the ureters and those of the genital ducts are to be regarded as landmarks of morphological permanence, it would appear that the muscular tube intervening between these, which in the cat constitutes the base of the bladder and the narrow but long urethra, with a somewhat similar development in the dog, is in the rabbit dilated to an equal calibre with that of the bladder above the ureters (cp. diagram, Fig. 11) and all serves for the storage of water.

The pelvic visceral nerves, when stimulated both together, cannot raise the pressure to a much greater height than 25 cm.; and contraction developes slowly, and is early fatigued. The main movement is always of the apical half of the bladder, the ventral wall of the lower half responding weakly, and the lower dorsal wall, that is the area limited headwards by the line joining the two ureters, is unaffected. Care is needed in the isolation of these nerves, lest the very delicate filaments of the pelvic plexus on the side of the rectum be injured and so an area of

[1] *Neurol. Centralb.* No. 14. 1904.

the bladder seem to be unconnected with the nerves. But the same distribution of the nerves was ascertained by stimulation of the sacral spinal roots without dissection of the pelvic plexus. Associated with the weakness of motor innervation is the fact that direct faradisation of the bladder wall does not initiate a sudden and strong contraction, as in the cat, but only a slow and slight increase of tone: moreover rhythmic changes of tension were never seen.

The hypogastric nerves are slender, but their stimulation has an invariable effect. The sheet of muscle between the ureters, that is the dorsal area of the lower half, contracts strongly and with fair speed, but it too shows fatigue early, much sooner than do the vasa deferentia. The ventral lower half, which was seen to contract when the sacral nerves were excited, gives no movement; and the curve of volume changes of the entire contents of the whole bladder was never of such a character as to suggest inhibition by the sympathetic nerves of the rest of the wall. Similarly intravenous injection of adrenalin produces only contraction of the dorsal area and of the sphincter.

These results do not agree closely with those stated by other observers. Budge[1] indeed remarked on the difficulty of inducing the rabbit's bladder to contract, and even in old bucks could not elicit a pressure rise of more than 9 cm. But Nawrocki and Skabitschewsky[2] from ocular observations described rabbits "deren Blase viel reizbarer ist als die der Katze." And Langley and Anderson[3] observed a "strong" contraction of the bladder when the sacral roots were stimulated. Langley[4] also ascribed to the sympathetic nerves an effect on the rabbit's bladder like that on its descending colon, being "contraction and inhibition of the whole muscular tissue of the organ."

As the bladder passes into the urethra beneath the symphysis pubis it is in both sexes encircled by a dense venous plexus, and crossed in front by a considerable mass of the obturator internus muscle. Though the former might, the latter could not control the passage. The urethra itself is lax and of the widest calibre; the vasa deferentia or vagina open upon it just within the venous plexus and 1 cm. below the upper edge of the symphysis. Immediately above this point, that is at the upper limit of the venous plexus, a sphincter is developed in its wall.

The anatomical arrangement of these parts places difficulties before the attempt to measure the resistance of the sphincter. Some experiments on its action were made by studying the resistance to outflow from the bladder, and others by placing within the sphincter a cylindrical balloon

[1] Henle's *Ztschr. f. rat. Med.* XXI. p. 174. 1864.
[2] *Pflüger's Arch.* XLVIII. p. 341. 1891.
[3] This *Journal*, XIX. p. 79. 1895.
[4] This *Journal*, XII. 1891. *Proc. Physiol. Soc.* p. xxiv.

recorder with rigid ends but flexible walls which would represent only the changes in the muscle in direct contact with them. Excitation of the hypogastrics always caused the sphincter to contract rapidly and with fair power, insomuch that in the rather doubtful measurements by resistance to outflow it could uphold a head of 40 cm. water. Adrenalin, when injected into the circulation, had a like effect, the indenting of the sphincter being very obvious to the eye.

The sacral nerves on the other hand inhibited the sphincter. The unavoidable exposure of the muscle during the dissection of the nerves, and the fact that the sphincter is always relaxed in the anæsthetised animal, made the demonstrable change of tension slight: still it was always observed in the first hour of an experiment.

The bladder of the rabbit may be regarded from the point of view of function as representative of a third type. It approximates to a passive receptacle. The main control of micturition is vested in the sphincter, whose contraction must be directly inhibited in order that the feeble walls of the bladder may expel what they enclose. The urethral passage, even in the male, is peculiarly wide and unrestricted, so that only a slight pressure is needed to expel the thick and somewhat gelatinous urine. But a powerful contraction of the sphincter by the hypogastrics is necessary in the female as well as in the male, for the vestibule is in more direct and wider communication with the urethra than is the vagina, the very opposite of the anatomical arrangement in the dog and cat.

With this general view of the action of the rabbit's bladder the experiments of Kupressow[1] and Ott[2] do not smoothly harmonise. By successive transections of the cord from above downwards, they found that the resistance to outflow fell suddenly when the section reached a level below the fifth or sixth lumbar vertebræ, that is probably when injury was done to the extradural roots of the sixth lumbar nerve, and to the intradural roots of the same and also of the seventh and the upper sacrals. But the spinal origin of the hypogastric nerves is chiefly from the fourth lumbar segment, and yet no control of the sphincter was indicated by a change in the resistance after injury to this region. Kupressow's measurements give a high value to the resistance, suggesting that the method of experiment did not fully distinguish between contraction of the sphincter and of the surrounding musculature which could influence outflow. The differences tabulated by Ott are slight. It may be supposed that the injury to the sacral cord, by excitation first inhibited the sphincter and then removed any obstacle caused by the striped muscles adjacent.

Masius[3] observed an escape of urine after transection of the cord at the second lumbar vertebra, and a continuous flow after destruction of the nerves underlying the sixth vertebra.

[1] *Pflüger's Arch.* v. p. 291. 1872.

[2] This *Journal*, II. p. 42. 1880.

[3] *Bull. de l'Acad. Royale des Sciences etc. de Belgique*, xxv. p. 495. 1868.

IV. The Ferret.

(*Mustela putorius, var. domestica.*)

The ferret's bladder is thick walled, of small size, and rarely exhibits rhythmic contractions. In response to excitation of the pelvic nerves it contracts forcibly, and the reaction can be evoked again and again with but little fatigue. The first sacral spinal roots together will raise the pressure to 45 cm.; the second pair contain rather fewer motor fibres, being incapable of a rise above 30 cm.

The peculiarity of the bladder in this animal is that it contracts in its entirety when the hypogastric nerves are stimulated. To the eye the contraction does not differ from that produced by the sacral nerves. Whether under isotonic or isometric conditions it is as rapid as the other, and it is well sustained without relaxation; but it does not attain to quite so high a maximum of tension. The parallel contraction by adrenalin was shown in a tracing published in an earlier paper[1]. A peculiar and inexplicable characteristic of the latter reaction is that it is prolonged for it may be more than 15 minutes, whereas that induced by the hypogastrics ceases with the stimulus. The prolongation is not due simply to the slight cold of exposure. An extract of the ferret's supra-renals produces the same result as adrenalin. Painted directly on the bladder wall, the drug causes a local contraction which does not irradiate over a circular area, but spreads along some bundle of fibres obliquely round the bladder so as to constrict it into an hour glass shape. Similar application in the cat causes only relaxation confined to the immediate neighbourhood.

Apart from the evidence afforded by the action of adrenalin, it can be proved by examining the spinal roots, that the contraction is effected by true sympathetic nervous impulses, not by vagrant sacral fibres that might be taking the road of the hypogastrics. In an animal in which the great sciatic nerve originated in the 7th lumbar and 1st sacral roots, the effective lumbar roots were the 3rd and 4th (*i.e.* 4th and 5th sub-costal), with a very slight action from the 2nd.

The tone of the bladder is not markedly depressed by section of either set of nerves. Anæmia[2], by obstruction of the abdominal aorta, causes the decentralised bladder to contract moderately.

[1] Elliott. This *Journal*, xxxii. p. 406. 1905.
[2] Cp. This *Journal*, xxxi. p. 165. 1904.

The sustained curve of the hypogastric contraction, like that in the dog and rabbit but unlike that in the cat, makes it improbable that inhibitor fibres should be lying side by side with the motors in these nerves. Yet when the bladder is in the prolonged contraction induced by adrenalin, the injection of ergotoxine causes abrupt relaxation by an immediate paralysis of the motor effect. And then adrenalin produces, as in the dog, pure inhibition: while the hypogastrics cause a diphasic curve as in the normal cat, the extent of contraction and relaxation respectively varying with the animal, with the dose of ergotoxine, and with the volume of the bladder.

The evidence is insufficient to appraise rightly the value of this argument from the action of ergotoxine. In the cat it is certain that the hypogastrics contain a few nerves causing contraction of a thin superficial sheet of muscle on the dorsal surface of the bladder, and a greater number which suffice to inhibit all the rest of the muscle. Adrenalin reproduces only the relaxation of the latter. Ergotoxine lessens the motor action and leaves inhibition unimpaired.

In the dog's bladder the hypogastrics supply nerves only to a small area at the base. Here ergotoxine converts the motor action of adrenalin into that of inhibition. Lastly in the ferret the original contraction by the hypogastrics extends over all the bladder and is simulated by adrenalin. Ergotoxine converts the response to either stimulus into inhibition. Is it to be believed therefore that inhibitor nerves are pre-existent in the ferret's hypogastrics and are revealed by paralysing the predominant motors? That does occur in the cat; and the explanation harmonises with what is known of the action of ergotoxine on other viscera. Or is the change to be interpreted by the analogy of the dog as being an actual inversion of nervous activity?

Whichever be the right answer, there is no doubt of the main fact, that the hypogastrics innervate a muscle which clothes the whole of the bladder, and that the normal reaction of this muscle to sympathetic excitation is that of forceful contraction. The peculiar band wise irradiation of the contraction from a spot painted with adrenalin suggests that the muscle concerned is an outer shell enveloping an inner mass which responds to the sacral nerves, that it is indeed a great overgrowth of the thin sheet described in the cat. Still such a hypothetical splitting of the bladder wall into two laminæ was not confirmed by any difference manifest to the eye between the results of the two modes of nervous excitation. That ergotoxine paralyses the hypogastric and not the pelvic contraction, does not touch the question at issue. To believe that one muscle fibre may receive motor nerves from two entirely separate sources is a difficult alternative, though supported on analogy by the current view of the double innervation of the salivary glands.

It would have been of great interest to examine the functional use of this hypogastric innervation; to learn whether it can evacuate the bladder after section of the pelvics, and whether the ordinary sympathetic constriction of the urethra is altered in order to facilitate such evacuation. But the experiments were not made.

V. Macacus Rhesus.

The bladder of this monkey is strong walled, but of much smaller capacity than that of the cat, holding at the utmost not more than 30 c.c. The urethra is short, and does not permit the bladder to rise out of the pelvis when distended. So the general anatomy resembles closely that of man. I am not aware of other observations on its nerve supply than those of Sherrington[1], who found motor nerves in both lumbar and sacral spinal roots, but saw inhibition neither in it nor in the cat.

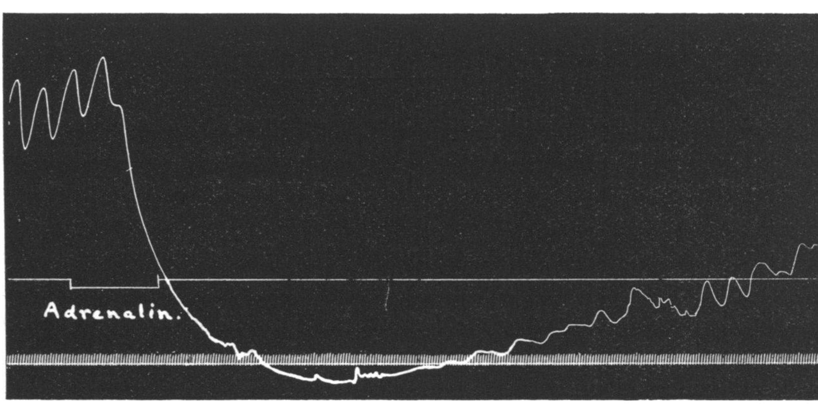


Fig. 9. Inhibition of bladder of monkey, Macacus rhesus, by adrenalin. Ether. Vagi, hypogastric, and pelvic nerves cut. *Volume changes* of bladder under constant pressure of 15 cm.

Inject 0·45 mgm. adrenalin into ext. jug. vein. Bladder relaxes from 10 to 26 c.c. and its rhythm is checked.

Stimulation of the hypogastrics produces a voluminal change of much the same character as that seen in the cat. First is a slight

[1] This *Journal*, XIII. p. 679. 1892.

contraction of 1 to 2 c.c. on a vol. of 20 c.c., and then ensues definite relaxation with arrest of rhythm. This relaxation with adrenalin reached the extent of 16 c.c. on v. 10, p. 15 (cp. Fig. 9). In the three experiments that I have made, inhibition by the hypogastrics was not so great: and to both the nerves and the drug the response soon failed. On a pressure record with constant volume of 10 c.c., the pelvics being uncut, the hypogastrics caused a fall from 21 to 13 cm. And both pelvics together (the dissection for these above the rectum being precisely the same as in the cat) on a vol. of 15 c.c. raised the pressure to about 40 cm., the rise being neither so rapid nor powerful as in the cat. The urethra was not examined.

The control of the bladder by the hypogastrics is therefore much the same in the monkey as in the cat. But the smallness of the initial contraction deserves note. It has been urged that the contraction at the base indicates a separate morphological platform, limited by the ureters, of motor sympathetic muscle on which the rest of the bladder has been raised. The ureters enter higher up the bladder in the macacque than in the cat. The anatomical platform therefore constitutes a bigger fraction of the entire bladder, and yet the contraction is proportionately less.

VI. Other Animals.

With the object of learning whether these several different forms of hypogastric innervation can be related to that kinship of mammals which determines zoological classification, a few experiments[1] were made on animals of other groups.

Indian Mongoose (Herpestes mungo). The bladder is small with a fairly long urethra, resembling anatomically, as does also the colon, that of the cat rather than that of the ferret. But physiologically it was like neither, for in the single experiment made the hypogastrics caused a very small contraction at the base, and so too did adrenalin. The direct application of adrenalin to the bladder wall had no effect. The pelvic nerves caused full and strong contraction, this being entirely confined to one side when one nerve alone was stimulated.

Indian Civet Cat (Viverra zibetha). Only one animal was examined, and it was in ill health. The bladder was of fair size (v. 40, p. 15 for body of 2,000 gm. ♀), but did not take so free an abdominal position as

[1] Some of these, by the kind leave of its Director, were made in the Wellcome Physiological Research Laboratory.

in the cat. Electrical excitation of the hypogastrics caused contraction of the bladder right up to its apex. The pelvic nerves had a similar effect. If there were any local difference of innervation it was that the hypogastrics caused especial contraction at the apex, and the pelvics at the base of the bladder: but the difference was probably due to differing exposure of the bladder at different times. Contraction with adrenalin was much less forcible than with the hypogastrics. Perhaps this may have had reference to the very poor health of the animal: yet the reaction of the blood vessels was not subnormal. Such contrast in efficiency between the chemical and nervous forms of excitation is the inverse of that for contraction in the ferret and goat, and for inhibition in the cat, monkey, and pig.

The Pig. An adult animal was not obtained. In each of two young females the bladder was found to be of large capacity. Stimulation of the hypogastrics produced only a slight contraction of the base, followed, as it seemed, by some inhibition. Adrenalin beyond a doubt caused full relaxation of all the body of the bladder. So in this animal the innervation, if analysed with greater care, would probably be found similar to that of the cat.

The Goat. The bladder is fairly strong walled, but of very small volume. In one animal, a large male of 30 kilog. and in rut, its volume was less than 100 c.c., barely exceeding in absolute capacity that of a large cat. The bladder exhibited no rhythm, and its tone did not depend on the integrity of the sacral nerves. After destruction of the sacral spinal cord, excitation of the hypogastrics reduced the volume of 40 c.c., p. 20, by one-third. Intravenous injection of 1 mgm. adrenalin caused its complete contraction at all points so that it assumed a curiously knobbed appearance. This contraction was not prolonged as in the ferret.

But the bladder of a female goat was found to be of distinctly larger volume, while it gave a contraction of but 5 or 6 c.c. on v. 90 when the hypogastrics were stimulated. And in a second female the intravenous injection of 1 mgm. adrenalin, after destruction of the lumbo-sacral spinal cord, caused a similar quick contraction of but 5 or 6 c.c. on v. 70. In both these the contraction was only of the base of the bladder, whereas in the male it had extended over all the surface. Here therefore, a difference must exist between the innervations of the bladder in the two sexes, that of the female resembling the arrangements in the dog, while in the male it is much as in the ferret. The contrast is not due to a growth of sympathetic muscle simply in connection with sexual activity, for the bladder of a castrated he-goat was found to react to adrenalin somewhat after the manner of the entire male. Thus 0·75 mgm. caused it to contract visibly everywhere, though only to the extent of 25 c.c. on v. 75, p. 25: stimulation of the hypogastrics could effect only a basal contraction of a few c.c. as in the female. After the injection of 20 mgm. ergotoxine 0·5 mgm. adrenalin excited, instead of contraction, moderate relaxation. The experiments were too few and incomplete to determine the anatomical nature of the changes in the male goat. In an old female sheep the reactions were like those of the female goat.

This cursory account of the various mammals suffices to remove the idea that a particular type of bladder innervation must be imprinted on every member of a zoological family. If not within the Viverridæ, at any rate in the Aeluroidea all three possibilities are exhibited by the cat, ferret, and mongoose respectively. The pig differs from the goat; and even the male goat is unlike the female.

But the differences of physiological behaviour are correlated with obvious differences in the bladders themselves. Thus the motor type of hypogastric innervation is associated with a bladder of small capacity that in the ferret certainly is evacuated with great frequency. Inhibition by the hypogastrics in the cat appears with an extremely large bladder. Its absolute capacity is about 80 c.c., more than $\frac{1}{40}$th of the body weight. That of a ferret is about 5 c.c., or $\frac{1}{120}$th. An average value for bladders of the indifferent type is about $\frac{1}{100}$th of the body weight. But in the macacque monkey hypogastric inhibition occurs, while the bladder volume is about 30 c.c. or $\frac{1}{70}$th of the body weight. Therefore great capacity is not indissolubly associated with and to be regarded as a certain indication of inhibitor nerves.

A second physiological characteristic of the bladders in which inhibition is manifested, is the large amplitude of their rhythmic contractions. These movements are often very conspicuous in tracings taken from the cat and macacque: they are faint in the dog, rabbit, and ferret.

Man. As zoological kinship has been shown to be of so slight determinant value for the varieties of bladder innervation, the nature of the hypogastric supply in man cannot be deduced from what was found in the macacque. Here the only methods of enquiry possible are those of direct experiment by painting the muscle with adrenalin, and of indirect deduction from the capacity and rhythm of the bladder.

The first I have had the opportunity of applying in a case, ♂, of moderate cystitis in which the bladder muscle did not seem to be much harmed. During exposure of the bladder in the first stage of the operation for suprapubic cystotomy, a solution of 1 : 2000 adrenalin was painted directly upon the muscle of its ventral surface. The muscle gave no manifest response. Plainly therefore the hypogastrics are not motor to all the bladder as in the ferret. Inhibition might be the true response, and yet have not been capable of demonstration under the conditions of this experiment. But the human bladder is small (± 350 c.c.), and it does not exhibit much rhythm[1]. From these characters and also from the subjective difficulty experienced in suppressing for long the desire of micturition, it may be inferred that the hypogastric nerves in man probably cannot inhibit the bladder to any marked extent[2].

VII. General review, including the innervation of the ureters.

Recurring now to the type studied first, it appears from this comparison that the cat possesses a bladder whose innervation has been developed to an exceptionally high degree of perfection. The pelvic nerves to it cause contraction of the entire bladder and relaxation of the urethra, movements adapted for the discharge of urine. On the other side the hypogastrics facilitate retention of urine by constricting the urethra, that is the sphincter of the bladder, and inhibiting the tone of the detrusor urinæ. From the point of view of function the two nerve trunks are completely antagonistic to one another (P $\pm$ and H $\mp$). In other animals the peripheral machinery for expulsion of urine is generally the same (P $\pm$), but that for retention is less highly developed and effects merely closure of the sphincter (H $+$). None the less the functional antagonism holds.

Such teleological adaptation governs throughout the visceral territory. The nerve trunk running to any particular viscus is a functional unit, bearing in one bundle the nerve fibres, motor and

[1] Cp. Plates I. and II. in Mosso and Pellacani's paper, *Archives Ital. de Biol.* I. p. 128. 1882.

[2] Absence of sympathetic nerves from the fundus of the human bladder is also suggested by the nature of the referred visceral pains of the distended bladder. According to Head (*Brain*, XVI. p. 84. 1893), the pain is referred to sacral skin areas alone, until ineffectual efforts at micturition are made, introducing pain in the 11th thoracic to the first lumbar skin areas, that is in the area corresponding to the hypogastric innervation of the sphincter.

inhibitor, which excite at the appropriate points of the sheet of plain muscle contraction and inhibition[1] in harmonious co-operation for this one function.

Double innervation of one organ by two separate trunks generally indicates double control, each for one of two opposed functions. Thus in the diagram (Fig. 10) of the innervation of the pelvic viscera in the

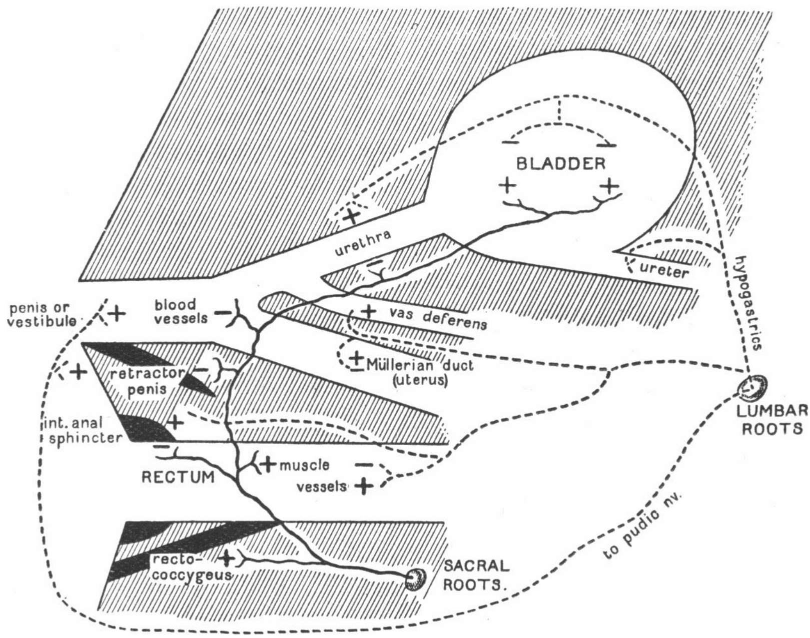


Fig. 10. **Diagram of the innervation of the pelvic viscera in the cat, illustrating the functional antagonism of the lumbar (sympathetic) and sacral visceral nerves (nervi erigentes). The sympathetic nerves are represented by the broken line. Contraction and inhibition are indicated by + and − respectively.**

cat it is shown that motor and inhibitor fibres appear indifferently in both hypogastric and pelvic visceral nerves, but that the reactions to either nerve trunk in any special area of muscle are generally antagonistic, and that each subserves definite and opposed functions. The sacral nerves effect the primitive visceral movements that are the first need of the animal, to wit voidance of the excreta. The hypogastrics represent later refinements, whereby these acts may be deferred to a

[1] A nervous co-ordination at the periphery which is in a manner comparable with Sherrington's central reflexes of simultaneous double sign. *The Integrative Action of the Nervous System.* London. p. 83. 1906.

moment better suited to the other activities of the whole animal; in the bladder for example closing the sphincter and relaxing the wall to accept its burden; in the colon doing the like[1] and further constricting the blood vessels lest general harm result by absorption of poisonous bodies from the contained residua of digestion. Only in the act of impregnation are the two nervous systems found to be synergist: and then the two unite in harmony, the sacrals by inhibition of the blood vessels and of the retractor penis preparing the required erectile structures, while the motor fibres of the hypogastrics expel the contents of the vasa deferentia and of the glandulæ vesicales and constrict the bladder sphincter lest the secretions be driven up the wrong path.

So the simple and obvious rule that connects the visceral movements and gives order to their apparent complexity is this of teleological adaptation,—the functional development of nervous ties between the C.N.S. and a muscular tissue depends on the daily need.

The ureters. Consideration of this view suggests that the innervation of the ureters cannot very well be of a powerful motor character, for full constriction of them is never required. Yet the most recent writers have described such an effect by the sympathetic nerves. Protopopow[2] indeed, disregarding the hypogastrics, did little more than suggest that the splanchnics augment peristalsis of the ureters in the dog. Fagge[3], also using dogs, described a motor effect of the hypogastrics on the ureters but obtained no result with the splanchnics: his tracings show that the first was at the best no more than an improvement of the peristaltic rhythm. And Stern[4] observed a similar accelerating effect of the hypogastrics in curarised dogs, while by the splanchnics slight inhibition was produced, and especially so after small doses of atropine. But Brodie and Dixon[5] state that "adrenalin excites a powerful contraction of the ureter," implying further a parallel response to stimulation of the sympathetic nerves.

[1] In an earlier paper (This *Journal*, xxxi. p. 157. 1904) I have described a good example of this functional adaptation, in which the sympathetic nerves, though inhibiting the muscle of the bowels in general, constrict a special ring at the ileo-colic sphincter. The distribution of the sacral nerves to the colon in different mammals was also shown to be limited to the final segment, which alone is to be emptied in defœcation. (*Ibid.* p. 272.)

[2] *Pflüger's Archiv*, LXVI. p. 1. 1897.

[3] This *Journal*, XXVIII. p. 306. 1902.

[4] *Thèse de Genève*, 1903. Quoted from Metzner's article in Nagel's *Handbuch der Physiol. des Menschen.* Berlin. 1906. Vol. II. p. 297.

[5] This *Journal*, xxx. p. 492. 1904. The authors have kindly informed me that the statement was not based on their own observations. It was apparently accepted by Henderson without experimental test (This *Journal*, XXXIII. p. 176. 1905–6).

The statement certainly cannot be applied to the ferret. In this animal the ureters exhibit an exceedingly powerful, regular, and enduring peristalsis which is not affected in any degree by adrenalin; nor could I detect any proof of its control by the sympathetic nerves.

The ureter of the cat is too small for instrumental record of its movements, and the fat overlying the tube hinders direct observation. Stimulation of the hypogastric nerves was seen to produce time after time a very manifest contraction of the base of the bladder: yet with it was no perceptible effect on the ureters at any point. They certainly did not shorten, and their rhythm of peristalsis was unchanged. Adrenalin was equally void of effect. However the difficulty of seeing the undoubted constriction of the urethra by adrenalin lessens the worth of these observations.

With the larger ureter of the dog and its very obvious peristalsis this objection disappears, and more faith may be given to what the eye sees. Every care was taken to avoid needless exposure of the ureter during observation and, except when it was desired to apply adrenalin, its fatty sheath was not opened lest nerves and blood vessels should be damaged thereby.

Exp. Large female collie dog, anæsthetised with A.C.E. Abdomen opened by crucial incision; hypogastrics cut and tied separately. Viscera covered with flannels.

10.40. Left ureter exposed as far as its swollen entry upon the bladder, but fatty sheath left intact. Peristalsis infrequent at the rate of five or six waves a minute, though each wave was typically complete. As the drop of urine came down, the ureter shortened and was lifted up to meet it. Immediately below the drop the tube relaxed completely, and through this dilated part the drop was shot, to be followed by instant and blanched constriction of all.

Stim. left hypogastric. Fair contraction at base of bladder, which was rapidly followed by constriction of the mouth of the ureter, the movement being passed quickly up the tube and leaving it a little relaxed in the rear. This reversed peristalsis was not heralded by the relaxation in advance seen with the forward movement. It occurred after a delay and, as it seemed, in sequence to the bladder contraction.

When the stimulus was repeated 10 or 15 seconds later, the bladder contracted once more but the ureter was irresponsive. A delay of at least a minute was needed for it to recover irritability.

If the hypogastric stimulus was thrown in during the passage of a forward wave over the ureter, it had no effect; but it could produce the reversed movement a few seconds after the passage of such a wave.

11.10. Adrenalin, 1 : 2,000, painted on ureter close to bladder. Certainly no contraction resulted, but the tube became rather relaxed. Over this flaccid area the wave of forward peristalsis was blotted out. And now stimulation of the hypogastric initiated the usual contraction of the bladder, but the backward wave in its turn was lost over the area of relaxation.

11.30. Ureter exposed close to left kidney, and the major splanchnic nerve cut. Stimulation of this did not clearly interject fresh waves upon the peristaltic rhythm already present. Local application of adrenalin relaxed the tube, abolishing both the peristalsis and the possibility of its production by the splanchnics.

12.0. Similar observations were made on the right ureter, that had not as yet been exposed. By squeezing, the bladder was irritated to contraction ; and then also the base of the ureter picked up the movement and transmitted a backward wave. On this side repeated stimulation of the hypogastric did certainly accelerate the existing rhythm of peristalsis.

Though the base of the bladder between the ureters and the collar around its front forming the sphincter could be clearly seen to contract when the hypogastrics were stimulated, the urethra below, which for the purpose of observation was distended with water by gently squeezing the bladder, contracted very feebly indeed.

From the experiment quoted and others it was abundantly clear that adrenalin in dilution had but little effect on the dog's ureter, and in concentration reduced it to flaccid paralysis. In cases where the ureter was already inert, the local application of adrenalin did not cause it to become flaccid, but paralysed considerably its normal power of reacting to a mechanical tap by quick local constriction.

The control by the sympathetic nerves was not determined. But while the simple method of observation was inadequate to detect subtle changes of rhythm, it could at least certify the absence of a powerful motor control. That was enough for the main point. Anatomically, as described for example in the dissection of Langley and Anderson[1], the ureters are united with branches of the sympathetic nerves: but physiologically the connection remains little more than a potentiality, for the mechanism of the urinary tract does not require that by it the ureters should at any time be firmly closed.

Physiologists freely recognise this principle of functional adaptation. But it must have material in which to find expression. Attempts have consequently been made to analyse it further by assigning the muscles which receive particular classes of nerves to sheets of separate morphological origin. None of these are, however, free from objection. Von Basch's law need not at present be discussed. But a fresh argument has recently been applied to the bladder, with the intention of proving that the distinction between the hypogastric and pelvic innervation is purely one of morphology. Starting from Langley and Anderson's generalisation, that the innervation of the internal generative organs is restricted to sympathetic nerves in contrast with the double supply to the cloacal derivatives, Fagge[2] used this to interpret Kalischer's anatomical distinction between the sphincter trigonalis and the rest of the bladder.

[1] This *Journal*, xx. p. 377. 1896.

[2] This *Journal*, xxviii. p. 304. 1902.

Kalischer[1] had inferred a dual ontogeny of bladder and trigone simply from the contrast in histological details between the two tissues. These, however, are no more than the imprint of differing function. The muscular fibres of the sphincter are closely compacted and the overlying mucous membrane is fitted to them with but little submucosa, because they never suffer so great linear elongation as must the muscle of the fundus. Fagge adapted the distinction to the results of his experiments on the dog, declaring that the structures derived from the Wolffian ducts (ureters and urethra) are innervated solely by the sympathetic while the reservoir developed from the urachus, or allantois[2]—a bubble

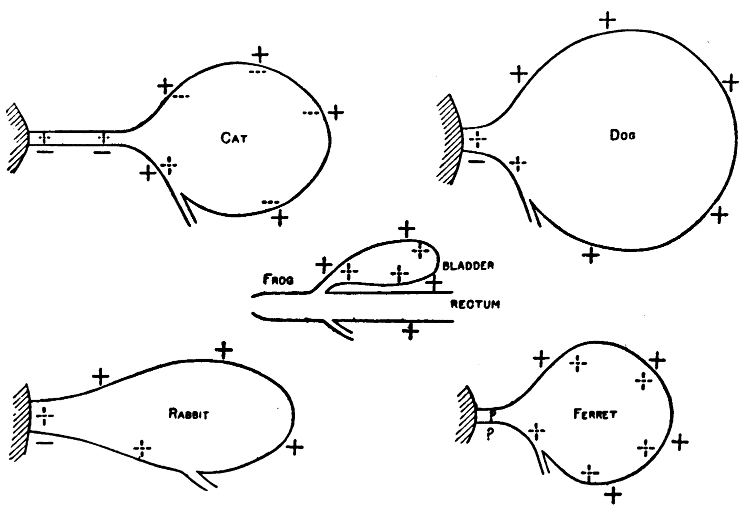


Fig. 11. Diagram of the innervation of various types of bladder and urethra. Level of entrance of ureters is shown, and the position of the genital ducts is indicated by the shaded mass of the prostate overlying the urethra. The distribution of the sacral nerves is given by the signs outside of the muscle, that of the hypogastrics by the broken signs inside the muscle wall.

[1] "Die Blase ist als ein später eingefügtes Organ zu betrachten, welches als Rèservoir in den ursprünglich aus Ureter, Trigonum, Urethra bestehenden harnableitenden Weg eingeschaltet worden ist; und ihrer Muskulatur kommt, zumal sie eine andere Entwicklung hat, vollständige Selbständigkeit gegenüber der Muskulatur des eigentlichen harnableitenden Weges zu. Es ist dieser Punkt wichtig für das Verständnis der physiologischen Vorgänge....Halten wir dagegen beide Muskelmassen somit für eine einheit, so hält es schwer, den Antagonismus, der zwischen beiden besteht, zu verstehen, und man kommt in die Verlegenheit, bei derselben Muskulatur zu gleicher Zeit verschieden wirkende Nerveneinflüsse annehem zu müssen." Kalischer, *Die Urogenital Muskulatur des Dammes*. Berlin. p. 155. 1900.

[2] The embryological history of the bladder and of the cloacal tissue is much disputed. Still, almost every writer emphasises the developmental continuity of bladder and urethra.

so to speak, blown on to the urethra—is innervated only by the pelvics[1]. The existence of inhibitor nerves he denied for both tissues.

This view may be at once dismissed. The hypogastric nerves do supply inhibitor nerves to the fundus of the bladder in the cat: and in the ferret their motor fibres embrace the whole bladder. Comparison of the various bladders in the diagram of Fig. 11 will realise how inconstant a fraction of the bladder is the so-called trigone below the ureters, and how widely beyond this limit may spread the influence of the hypogastric nerves.

The case of the frog and toad is of especial interest in regard of this question. In these animals the bladder is a ventral outpouching from the rectum (cloaca; Gadow's urodæum ?), while the ureters open quite separately into the dorsal surface of the rectum. The bladder would therefore appear to be of a purely cloacal type, free from all connection with muscle of the Wolffian ducts. Yet the sympathetic nerves have been proved[2] to cause a weak contraction of it even up to the apices.

Still, though the theories hitherto advanced have been proved unsound, their aim is not visionary. It must be possible to analyse the double innervation of the viscera and at last to point out the original nature of the tissues within which functional adaptation has wrought the complex harmony.

A first requisite is to ascertain the morphological value of the inhibitor nerves. Gaskell[3] was inclined to embrace these in general

Keibel (*Archiv f. Anat. u. Physiol.* 1896, *Anat.* p. 55) derives bladder, urethra, and sinus urogenitalis alike from the cloaca.

[1] Thus precisely inverting the old view, of Longet for example 1842, that the sympathetic nerves supply the bladder above and the sacral ("spinal") its neck below—an inference from topographical relationship and resting on no experiments.

[2] Horton Smith (This *Journal*, XXI. p. 101. 1897) and Dale (*ibid.* XXVII. p. 355. 1901) observed contraction of the bladder on stimulating the 7th and the 9th and 10th spinal roots in the frog and toad. No effect was obtained with the 8th. Apparently the 7th corresponds to the lower limit of the sympathetic outflow of mammals, and the 8th spinal to the gap of the hind limb nerves from which visceral fibres are absent. Dixon noted the corresponding contraction induced by adrenalin (This *Journal*, XXX. p. 493. 1904). It is feeble, like that by the 7th nerves and quite dissimilar from the quick and powerful movement induced by the 9th and 10th. I am indebted to Mr Dale for the demonstration of these experiments.

Information is much needed of the distribution of nerves to the single cloaca of such animals as the crocodile, with its three successive chambers of coprodæum, urodæum, and proctodæum (Gadow, *Phil. Trans.* 1888. CLXXVIII.). In mammals it is as though the coprodæum had acquired a separate opening at the anus, short circuiting the path through urodæum and proctodæum and leaving these to be differentiated into bladder and sinus urogenitalis.

[3] This *Journal*, VII. pp. 34 and 40. 1886.

within a "separate and complete nervous system" of their own. That opinion seems no longer tenable in view of the arguments based on the similarity of the nervous conducting paths[1] and also on the common action of adrenalin at the periphery. Motor and inhibitor nerves both occur within the class of the sympathetic nerves. They are exhibited in the organ innervated in two categories:

(i) Both + and − fibres belong to the sympathetic class, controlling the muscle to the exclusion of all other nerves. Such occur in the uterus[2]; and it may perhaps be argued from the action of ergotoxine that they exist also in the wall of the blood vessels.

(ii) One set of nerves, either + alone or − alone, comes from the sympathetic and the other of opposed sign from the sacral or cranial.

A notable instance of (ii) is given by the detrusor urinæ of the cat's bladder. Fundamentally this receives motor fibres from the sacral roots. But the same muscle is inhibited by sympathetic fibres. The evidence justifies the belief that this second control of the muscle has been recently developed. On the isolated neurone theory these inhibitors might be ascribed to a special outgrowth of new nerves from the C.N.S. to the muscle; and with this theory, in its baldest expression, there might be little difficulty in transferring the goal of sympathetic fibres from the urethral trigone to the detrusor urinæ, with change of sign of the muscular response. Gaskell has criticised the irrationality of this theory, and given in lieu of it an account of muscle and nerve developing ever in unbroken continuity as one great syncytial network[3]. His teaching therefore regards innervation as a sure guide-post up the path of morphogenesis.

Accepting it, but adding the possibility of side branches arising from any nerve fibre, as suggested by experiments described on pp. 421 et seq. of this paper, one may conceive the development of inhibitor control of the detrusor by branches springing from the postganglionic motor fibres to the trigonal muscle[4]. The conjecture stands unproved. If made good,

[1] Cf. Verworn, following Langley, *Archiv f. Anat. u. Physiol.* 1900. *Physiol. Supplem.* p. 105.

[2] Dale, This *Journal*, xxxiv. p. 187. 1906: and Cushny, *ibid.* xxxv. p. 1. 1906–7.

[3] *Journal Anat. and Physiol.* xxxix. p. 378. 1905.

[4] I have given elsewhere (This *Journal*, xxxiii. p. 436. 1905) the argument from the action of adrenalin, suggesting that it is the condition of the muscle which has determined, somehow or other, whether its response to the nervous impulse shall be + or −.

The anatomical form of this scheme would then suit the theories of Von Uexkull and especially of MacDougall upon the reciprocal relation of contraction and inhibition, as being caused by drainage of "neurin" to and from the irritable tissues. But these the principle concerned could be applied to the analysis of many other inhibitor actions of sympathetic nerves. Generally in these, inhibition is associated with a weak contraction. Such is the case in the mammalian intestine. It may be that here the contraction is of a primitive muscle sheet in connection with sympathetic nerves, whose original trunk has been almost wholly replaced by its inhibiting side branches to muscle of a different category, just as conducting tracts in the C.N.S. swell and dwindle as the tide of nervous impulses sets this way and that. In the amphibian and bird the control of the small intestine by the sympathetic is predominantly motor. But the relationship of the mammalian to these earlier types might be explained by (i) almost as well as by (ii), since nothing is known as yet of the possible inversion of muscular response to any given nerve without actual replacement of one tissue by another.

Until such information shall have been accurately obtained, it is therefore impossible to use innervation as means for demonstrating at once the ontogenetic source of the muscle of an organ. The inhibitor innervation may be primary or secondary. It seems, however, to be a reasonable assumption that in general the nerve which evokes a motor response is the aboriginal nerve of a muscle system. The habits of the aboriginal may be changed, as in class (i): it may live side by side with, or be utterly replaced by an intruder. Hence the ordered complexity of visceral innervation in the mammal.

A caveat must here be entered against a corollary that is liable to be based upon the morphological argument used above. It is to assume an inverse rule, namely that muscular structures which are known to be of common embryological parentage must be similarly innervated. But the common source cannot be used to indicate more than a connection with certain nerves. The development of these ties, whether it shall be "trophic" or be made the instrument of motor or inhibitor nervous impulses, is governed by the requirements of the individual organ and must be studied in each particular case.

As for the bladder the position may be summarised dogmatically. The fundamental muscle is a detrusor belonging to the sacral nerves, which are motor to it in all vertebrates: this muscle may receive secondarily inhibitor nerves from the sympathetic. Spreading up from the urethra, in all cases as far as the insertion of the ureters

theories do not explain *peripheral* inhibition. Adrenalin will inhibit the bladder when all its nerves are gone. Cp. Sherrington, *The Integrative Action of the Nervous System.* London. p. 203. 1906.

and apparently in some species over the whole surface of the bladder, is a superficial sheet of muscle belonging to the sympathetic nerves which cause its contraction. Perhaps from this latter muscle-nerve system have originated the occasional inhibitors to the detrusor. But it cannot be argued that this muscle must have been derived from the Wolffian ducts, for a similar motor reaction is exhibited by the cloacal type of bladder in the toad.

PART II.

RESULTS OF DEGENERATIVE SECTION OF THE VARIOUS NERVES TO THE BLADDER.

In this second half of the paper are described some of the changes induced in the cat's bladder by degenerative section of each of the nerves to it. Three aspects of the question have to be borne in mind. First, to what extent the "tone" of this doubly innervated sheet of muscle is a resultant drawn between the two opposed nervous actions, so that after removal of one set the antagonist imprints its power on the muscle. Secondly, whether removal of one part of the nervous machinery can be compensated for by the remainder taking up the burden of foreign activity. Thirdly, whether there is any essential difference in the vital activities of the muscle when decentralised (by section of all its preganglionic nerves) and when deganglionated (by removal of the ganglia and degeneration of the postganglionic nerves).

All the experiments were made on the cat. The normal innervation of the bladder in this animal may be summarised again for convenience here. From the 3rd and 4th lumbar spinal roots issue most of the nerves which pass by the inferior splanchnics to the inferior mesenteric ganglia. These sympathetic nerves effect inhibition of the entire bladder, constriction of the urethra, and contraction of a thin superficial sheet of muscle adjacent to the ureters. The ganglion cells of both sets of fibres are placed almost all in the inferior mesenteric ganglia: from these pass the right and left hypogastric nerves to mingle in the vesical plexus on the wall of the bladder. There are very few sensory afferent nerves in these trunks[1]. Mainly by the 2nd and 3rd sacral spinal roots arise the nerves which constitute on each side the trunk of the pelvic

[1] About 100 fibres in all from the total visceral area innervated. Langley and Anderson. This *Journal*, XVII. p. 186. 1894.

visceral nerve (nervus erigens). These effect contraction of all the bladder and relaxation of the urethra. The ganglion cells lie in the vesical plexus close to the muscles concerned, so that the postganglionic fibres can be found only upon the walls of the bladder. The main path of sensory impulses from the bladder is by these trunks[1].

I. THE INFERIOR SPLANCHNICS.

These preganglionic nerves from the spinal cord were cut in two experiments. Thereby the neurons constituting the hypogastrics were isolated from the C.N.S., but otherwise unhurt.

(i) In the first cat, eight days after section of the nerves the tone of the bladder under ether was high, v. 15, p. 15. This fell only to v. 30, p. 15, when the pelvics were cut: and a deep rhythm, that had been present, disappeared at the same time. Stimulation of the hypogastrics caused fair contraction and inhibition. Adrenalin did not enlarge the volume to more than 35 c.c. The pelvics, if excited by moderately strong currents, produced a normal contraction; but when a somewhat weaker stimulus, approaching the minimal value for maximal contraction in a normal bladder, was used, the contraction fell short of maximum and under either isotonic or isometric conditions proceeded with difficulty by jerking steps instead of by a smooth ascent.

(ii) In the second case, 14 days after the operation the bladder also exhibited fair rhythm with high tone, v. 40, p. 18, though it did not relax further when the pelvics were cut. Adrenalin or excitation of the hypogastrics alike caused fair relaxation to a maximum volume of 55 c.c. Stimulation of the pelvics had the same effect as that described in (i), normal for strong stimuli but by halting steps with the weaker.

A peculiar reaction to ether was also observed. The muscle and nerve system of the normal bladder is not affected very evidently by this anæsthetic. Here the animal's brain had been destroyed in order to make the experimental examination, and no ether was given: the volume of the bladder, both pelvic nerves having just been cut, was then 40 c.c. under p. 18. But each time that ether was administered, by 25 breaths of ether freely mixed with air and taken in one minute, the volume narrowed steadily to 25 or 20 c.c., returning to the old value with relaxation of the muscle in the next two minutes when the ether

[1] According to Langley and Anderson they carry more than 1000 afferent fibres each from all the pelvic visceral area. This *Journal*, XIX. p. 377. 1896.

was discontinued. From this it is evident that the anæsthetic in itself is partly responsible for the differences of tension recorded after different lesions of the bladder nerves. The muscle under these abnormal conditions is irritated by ether, whether directly or indirectly through stimulation of its peripheral nerves, and passes into a state of higher tension. Henceforward all the measurements given, unless stated otherwise, are from experiments made so far as possible under uniformly comparable conditions of ether anæsthesia.

Preganglionic section of the inhibitor nerves, then, induced a permanent rise of the "tone" of the bladder muscle, in which state it lost its supple readiness of response to nervous control either in the direction of contraction or relaxation. It will be seen that the change is of the same character as that following section of the hypogastrics themselves, but less profound.

II. The hypogastric nerves.

These were both cut by a lateral lumbar incision without opening the peritoneum or exposing the bladder. The section removed most of the postganglionic inhibitor nerves of the bladder and of those constricting the urethra.

The cats manifested no inability to retain urine. Micturition may have been rather more frequent, but the point was not closely observed. At intervals varying from three days to seven months after the first operation the cats were anæsthetised, and the reaction of their bladders determined. These experiments were made at various times, and not all for the immediate purpose of this paper: consequently the condition of the bladder was not determined with the same detail in each.

In five out of six cases the bladder was found to be in high tone and almost undisturbed by rhythmic contractions. For example on the sixth day, when the cut nerves must have degenerated almost completely, the tone of the arhythmic bladder was very high, v. 15, p. 15; and even after both pelvics had been cut, only 25 c.c. under p. 23. A normal bladder would then have relaxed perhaps to 80 c.c. Neither by extreme pressure nor by the inhibiting influence of adrenalin could the muscle fibres be extended to admit a greater volume than 30 c.c. And just as they would not admit of elongation, so too their shortening in a rapid isotonic contraction induced by the pelvic nerves was lost, though these nerves evoked an almost normal rise of pressure. From contraction of either form the relaxation was slow.

Even in the lapse of seven months, when partial regeneration of the hypogastrics was ascertained, the capacity had not increased beyond 50 c.c. under p. 20 with cut pelvics. But with this longer interval after the operation the muscle responded to stimulation of the pelvics quickly and well. A single exception was one of 63 days' degeneration, in which the bladder muscle behaved in a quite normal way. Unfortunately in this it was found that the catgut of the deep stitches had been infected with some organism, and by an oversight the hypogastrics were not tested for regeneration.

As the muscle early after section of both hypogastrics had been found to be disabled for good contraction by the pelvic nerves, a single hypogastric was severed in one experiment and later each pelvic nerve proved. That on the side of the lesion was a little less efficient, but no very clear difference was observed between them. The bladder was of normal capacity, v. 75, p. 12; and the surviving hypogastric produced in it the usual response.

A survey of the six experiments is given in the subjoined table.

Summing these results the main change produced, as seen in the etherised muscle, was as follows. Deprived of its inhibitor nerves the muscle of the bladder slowly contracted to a high level of tone. At this it rested with but little rhythmic movement. Preganglionic section of the pelvics brought it down but little, if at all. Their stimulation caused less forcible contraction than usual, and the relaxation to the original level was slow. The muscle was accessible to the inhibitor influence of adrenalin (cp. Fig. 12), as well as to the motor impulses by the pelvics. But its fibres were less elastic: changes of length were much less easily evoked than changes in tension. Later, with regeneration of the hypogastrics, it obeyed the motor nerves with greater flexibility and speed, and so too yielded more fully to adrenalin[1].

It should be noted that these changes were not caused merely by cessation of inhibitor impulses from the C.N.S., for, though of the same

[1] Relaxation by adrenalin was so diminished in the first ten days as to make it appear at first sight dependent on a stimulation of the true "nerve endings" of the hypogastrics; vanishing accordingly with their degeneration. The question has been discussed in another paper, where it was also shown that denervated muscle reacts to adrenalin, as it does in general to any excitant chemical stimulus, with increased sensitiveness of *contraction* (This *Journal*, xxxii. p. 441, 1905). The converse lowering of sensitiveness in this instance of *inhibition* probably is not to be referred to an exceptionally depressed sensitiveness of the myoneural junction, but to alterations in the reacting muscle fibre which were otherwise evidenced by the tardiness of its response to the pelvic motor nerves.

Interval after section of the hypogastrics	General tone of the bladder	Result of stimulating both pelvic nerves	Action of adrenalin	Remarks
3 days	Very slight rhythm, high, v. 15, p. 15; and only slightly relaxed by section of the pelvics.	Almost normal response in isometric contraction.	0·3 mgm. injected; no effect. 0·6 mgm.; slowly relaxed by 3 c.c. to 20 c.c.	—
5 days	Slight rhythm, high.	Both, coil 10, caused contraction of 18 c.c. on v. 35, p. 15, *i.e.* subnormal.	0·3 mgm.: no effect.	—
6 days	No rhythm, high, v. 13, p. 15; not relaxed by section of the pelvics.	Good isometric contraction to 55 cm., very poor isotonic contraction, *e.g.* of 6·5 c.c. on v. 22, p. 20, and sluggish relaxation.	0·3 mgm.; relaxed very slowly by 9 c.c. to 31 c.c. But the drug lowered the tension of the muscle, and depressed for long its response to stimulation of the pelvic nerves[1].	Maximum volume possible was little more than 30 c.c. instead of 80 c.c.
9 days	Slight rhythm, high, v. 20, p. 15; unchanged by section of pelvics.	Good isometric contraction. Nerves seemed swollen.	0·2 mgm.; very slight effect.	—
63 days	Low, v. 70, p. 13.	Very good contraction under both conditions.	0·3 mgm. caused complete relaxation.	Quite normal reactions. Hypogastrics were not tested for complete section. Deep stitches had been infected.
210 days	Slight rhythm, high, v. 30, p. 20; but relaxed to v. 55, p. 20, when pelvics were cut.	Very good contraction.	0·12 mgm.; full relaxation.	Hypogastrics had regenerated to + and − effect, but were soon fatigued.

[1] Cp. Fig. 11. This *Journal*, XXXII. p. 442. 1905.

character, they were much less marked when the path was broken in its preganglionic course. And perhaps the contrast in respect of rhythm—its presence with the inferior splanchnics cut and its absence after section of the hypogastrics—may be simply ascribed to the greater rigidity of the muscle under the latter condition.

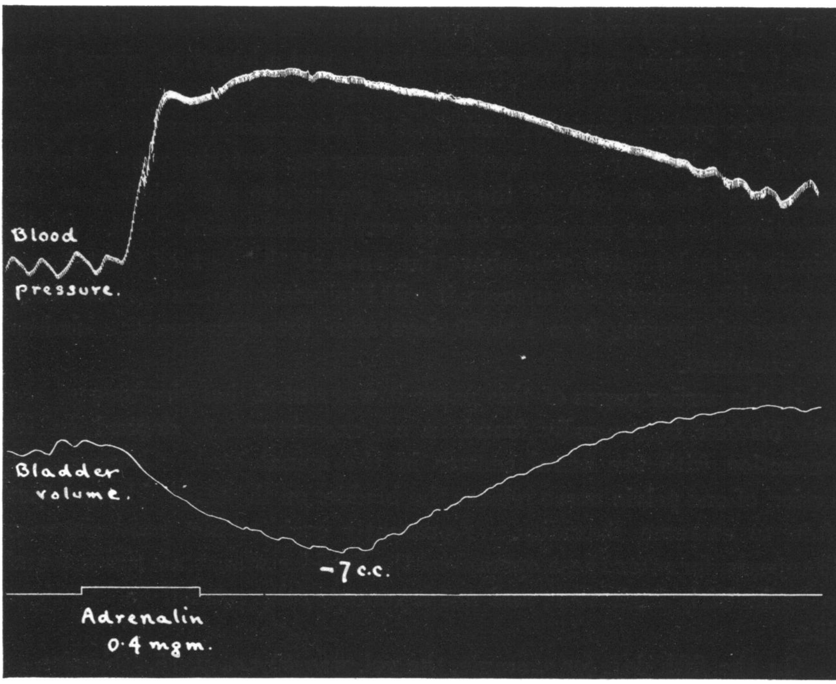


Fig. 12. Cat's bladder. Volume changes under constant pressure of 20 cm. Hypogastric nerves had been cut ten days ago. Tone of bladder high, vol. about 25 c.c., p. 20 cm.

Inject 0·4 mgm. adrenalin into ext. jug. vein: bladder relaxes slowly and to the extent of only 7 c.c.

This tracing is taken from another experiment than those summarised in the table, because the blood-pressure was not recorded in any of the latter.

Whether the nervous lesion were pre- or postganglionic, the inhibitor myoneural junctions still persisted so that the muscle was still accessible to the influence of the secretion of the suprarenal glands. That, however, was insufficient. It therefore seems probable that the slight "tonic" inhibition, which is needed to preserve the normal suppleness of the cat's bladder, can be maintained only when that muscle is in connection with the proper peripheral ganglion cells.

With narrowed volume and shallow rhythm the cat's bladder, after removal of the inhibitor nerves, resembles those of the other mammals from which inhibitor nerves are congenitally absent.

III. One pelvic visceral nerve.

In twelve experiments the right nerve was cut above the rectum close to its origin from the sciatic plexus, and a length of about 1 cm. removed as far as the branching at the first rectal ganglion. Thereby the motor preganglionic to, and most of the sensory nerves from, one side of the bladder are caused to degenerate: but the other bladder nerves and the ganglia of the vesical plexus are not injured, as the operation does not expose or in any way interfere with them. If the skin incision be made well above the anus at the root of the tail and closed with separate silk sutures, it will heal without dressings or delay. At intervals varying from 4 to 60 days after the operation the bladder was examined.

In the earlier pages of this paper it was stated that the tone of the cat's bladder is generally found in an experiment to depend on its connection with the sacral centres in the spinal cord. Consequently section of one pelvic nerve relaxes the bladder on the same side, and that often to extreme flaccidity. Apparently such atonic paralysis soon disappears, for after these operations the bladder was at all times found to be in fairly high tone, and not asymmetrically relaxed on the right side.

On the fifth day, for example, the vol. was 40 c.c., p. 15. Section of the left pelvic nerve did not increase the volume. The muscle of this left, or normal side was therefore in a state of exaggerated tone. When caused to contract by stimulation of the pelvic nerve, it relaxed more slowly than usual. Even brief exposure to air excited its contraction rather more readily than in the normal bladder: and the reaction could be produced after section of the left pelvic nerve. An equal contraction was developed on the right side by exposure. At this time, then, the general tone of the muscle was slightly increased on the decentralised as well as on the uninjured side. But the increase was not great, for the muscle was perfectly supple and reacted with extreme ease to adrenalin while it provided a perfect illustration of inhibition by the hypogastric nerves.

Thus four days after the operation the two hypogastrics, stimulated with a weak interrupted current that was easily bearable by the tongue, caused on v. 40, p. 15, a contraction of 8 c.c. and then relaxation of 45 c.c. A difference in condition between the two sides of the bladder was illustrated by the different extent to which either was relaxed by stimulation of these nerves. In the instance named first of five days' degeneration, the right hypogastric, that is of the side on which the pelvic nerve had been cut, caused a contraction of 3 c.c. and relaxation of 27 c.c., whereas the left relaxed the bladder to the extent of only 10 c.c.

This peculiar aptitude for inhibition after decentralisation of the motor nerve[1] proved of value for the analysis of inhibition by the hypogastrics, for it was not lessened by the action of nicotine on the muscle. Thus in the experiment from which Figs. 13 and 14 are taken, 18 days after section of one pelvic, the hypogastrics on v. 15, p. 15, induced contraction of 3 c.c. and relaxation of 30 c.c.: after the injection of 20 mgm. nicotine[2] the same stimulus gave + 3 c.c. and − 27 c.c. respectively. By this test and by the results of degenerative section of the inferior splanchnics, it is proved indubitably that the cell relays of the inhibitor nerves lie chiefly in the inferior mesenteric ganglia.

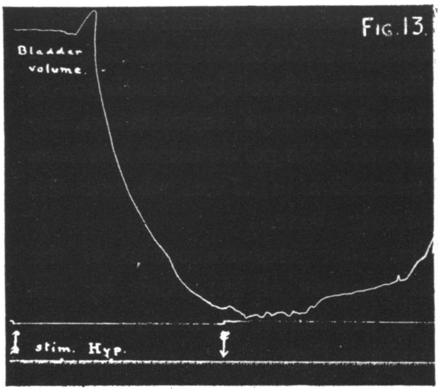
In this last case the tone of the muscle was higher, and its inhibition by the hypogastrics less extensive than in the first week. Such further increase of tone during the second week was always observed, and associated with it was yet slower relaxation from the contraction following excitation of the left pelvic nerve. Now too another change was becoming prominent.

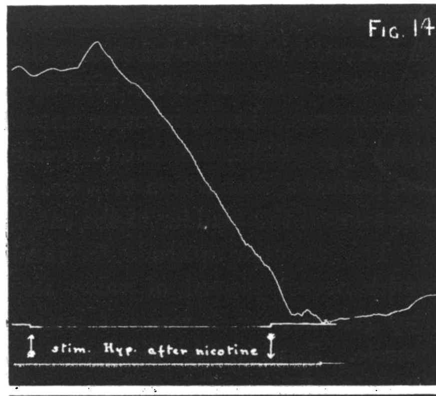
Ordinarily stimulation of one pelvic nerve results in a contraction that is almost confined to the same side of the bladder[3], and transgresses the line of the median blood vessel by only a few millimetres. This was the case too in the operated animals up to the 9th day: the left pelvic produced a purely ipsilateral contraction, which showed no abnormality except in that the relaxation from it was a little slow. But on the 12th

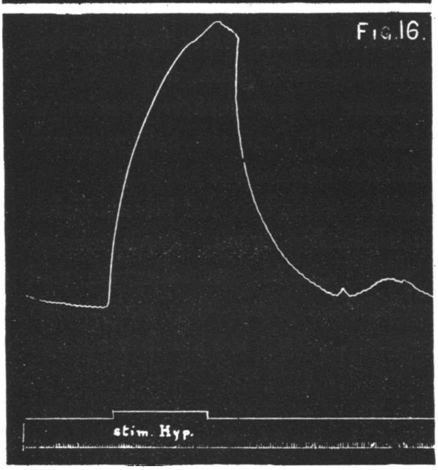
[1] This method of emphasising the action of an inhibitor nerve on a doubly innervated sheet of muscle is important. It is only through it that a good demonstration of inhibition by the hypogastrics can be undertaken with assurance. Perhaps it is of wider application: for example the action of the splanchnics on the stomach, which has eluded the observation of some workers, might so be shown with ease.

[2] The action of nicotine on the decentralised bladder often departs a little from normal. Properly the excitation induced by the stimulation of the ganglion cells with this poison is brief, and the bladder relaxes fully. Decentralisation seems to give excitation superior influence over paralysis. The contraction may in such case often be excited again by a second or even a third injection of nicotine; and the form of the curve, instead of being simply up and down, is that followed by a rapid recovery to fairly high tone.

[3] Cp. Sherrington. This *Journal*, XIII. p. 683. 1892: and Langley and Anderson, *ibid.* XIX. p. 80. 1896.







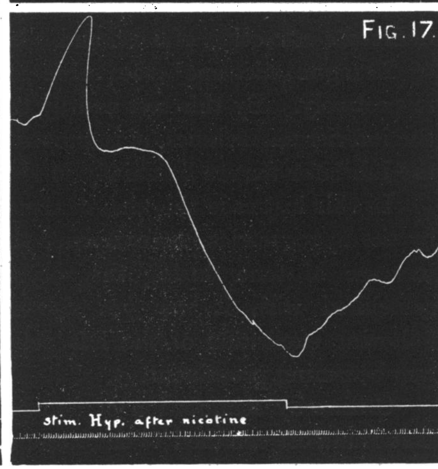


Fig. 13. Cat. Right pelvic visceral nerve cut 18 days previously. Isotonic record of bladder vol. under p. 15 cm. Bladder not exposed: left pelvic untouched, but hypogastrics cut across. Tone of bladder high and no rhythm. Stim. hyp., coil 10: result + 3 and − 30 c.c. on v. 15 c.c.

Fig. 14. Same experiment as preceding figure. Nicotine, 20 mgm., was injected, and four minutes later the hypogastrics stimulated. Result + 3 and − 27 c.c.

In the same experiment it was also proved that the local application of nicotine to the inferior mesenteric ganglia paralysed both the motor and inhibitor nerves alike.

Fig. 16. Cat. Bladder volume under constant pressure. Both pelvics cut 46 days previously. Ether. Hypogastrics cut laterally; spinal cord destroyed from fifth lumbar segment to coccyx; and bladder not exposed. Largest Brodie volume recorder, giving instrumental records identically comparable with those of Figs. 13 and 14.

Stim. hypogastrics, coil 12·5 cm., *i.e.* weak; rapid contraction of 30 c.c. on v. 110, p. 8, sustained until stimulus ceased. A few minutes later mere pulling on these nerves caused a prompt contraction of 70 c.c.

Fig. 17. From same experiment as Fig. 16. Nicotine, 30 mgm. in all, had been injected. Fifteen minutes after the last injection, of 10 mgm., the hypogastrics were stimulated, coil 8 cm. On v. 80, p. 9 bladder contracted 11 c.c., and then with a pause relaxed 22 c.c. below original level.

or 13th day the opposite side also joined in the contraction, though weakly and with a little delay.

After five weeks the contralateral effect was well established, and did not differ in either time of onset or strength from the ipsilateral movement. The whole bladder contracted instantly. But the relaxation was slow. Really the tone was now lower than in the second week; but the increasing contracture and the exalted irritability in respect of exposure to air generally made the bladder appear to be in high tone, *e.g.* v. 20, p. 15, that was not lessened by section of the left pelvic. The muscle was not hypertrophied on either side. Each hypogastric affected the muscle with equal power; and indeed the earlier difference between them was only demonstrable in cases where the action of the left pelvic was confined to its own side.

From the interval, 12 days or more, needed for the appearance of the contralateral response, it seems probable that it is determined by the growth of some new conducting path. This might be by:

(i) Conduction through the unstriated muscle.

(ii) Budding of postganglionic nerve fibres to the muscle.

(iii) Budding of preganglionic nerve fibres to the contralateral ganglion cells.

(iv) Facilitation of a pre-existent but disused nervous path. Or the phenomenon might be explained by:

(v) Exaggerated irritability of the decentralised ganglion cells, which would lead to their exploding a contraction on their own side in response to the detonation of the other.

The contraction was observed under conditions of volume change without appreciable rise of intravesical pressure, so that mechanical rise of tension at least could not be the detonator. Stimulation of the great postganglionic nerve trunks on either side of the bladder caused a powerful contraction that was strictly limited to the normal area of distribution of the trunk. And direct faradisation of the muscle at any point resulted in a localised contraction that extended over a smaller area than in the normal bladder. The decentralised system was therefore not more, but less irritable toward mechanical and electrical stimuli (though more so to cold); and (v) could hardly be accepted to explain the phenomenon.

Further, (i) was also to be set aside for these same reasons and also because, as shown later, the contralateral response was not developed even in the lapse of 22 days when the ganglion cells of the decentralised side had been torn out.

Division of the muscular coat of the bladder in the middle line from apex to the plane of the ureters both in front and behind did not annul the contralateral effect of stimulating the left pelvic. But the response vanished after injection of nicotine into the blood vessels. Then, the ganglion cells being blocked by the poison, stimulation of the post-ganglionic nerves on either side of the bladder caused as before contraction only in the proper area of distribution of each nerve.

From these observations it is clear that the path of conduction lies in the base of the bladder; that it is preganglionic, and consists in the functional development of ties between the left pelvic nerve and the right ganglion cells The choice is therefore restricted to that between the explanations (iii) and (iv).

The assumption most obvious to make is (iii), that branches had budded from the sound fibres of the left side to the decentralised cells on the right, the buds being perhaps encouraged by a chemiotactic influence of the widowed cells. But such a budding, though probably analogous to the method of development of collateral fibres in the C.N.S.[1], would require for its acceptance a departure from the belief that the generation of peripheral nerves in adult life can only be from the ends of injured nerves, and not by a branch from sound fibres.

The alternative explanation (iv) supposes that in both pelvic nerves are potentially present preganglionic fibres which may affect the ganglion cells of both sides, but that the contralateral system tends to great physiological resistance. Such a theory would be justified by the fact that the bladder developes from a tube in the mid-ventral line of the body, and not by the fusion of lateral tubes, as in the formation of the cat's uterus where the innervation by the vaso-constrictors remains so sharply limited to each original half.

But the cause of the assumed differential atrophy is hard to conceive. In kittens seven days old I found the ipsilateral effect of each pelvic to be as restricted as in the adult. Moreover the strongest stimulation of the nerve does not break through the supposed paths of greater resistance and affect the opposite side a whit more widely than do moderate stimuli. There is proof too that the paths down which the impulses travel to the opposite muscle are not provided by independent and

[1] A like growth too—unless splitting and migration of the ganglion cells be assumed—must have occurred in the phylogeny of the abdominal sympathetic chain. Langley (*Brain*, XXVI. p. 17. 1903) remarks that the preganglionic fibres of fishes are almost restricted to their own segmental ganglia. But in mammals a preganglionic axon may communicate with cells in several successive ganglia of the chain.

separate fibres, but almost certainly by branches from the normal fibres in the left stem. This is proved by the axon reflexes that may be demonstrated when the contralateral effect has been established. They are of the following nature.

The right pelvic nerve has suffered degenerative section. If the postganglionic nerve bundle on the left or normal side be now picked up from the wall of the bladder, cut close to the muscle, and then dissected off a little way backward to the ganglia, its excitation causes the decentralised right side to contract with power that increases as the electrodes are moved further up the left nerve past the main ganglia, though it is never so great as that seen when the left pelvic trunk itself is excited. This result is still obtained, if the left pelvic trunk be cut across close to its origin from the sacral nerves; and it is therefore independent of reflexes from the C.N.S. And now peripheral stimulation of the main left trunk causes the right side to contract by impulses travelling down the new path, whereas it does not affect the left side to which the normal path has been interrupted beyond the ganglia.

In another bladder an attempt was made to excite the converse reflex, namely contraction of the left side by stimulation of the nerves lying on the right wall: but this failed.

This preganglionic axon reflex proves that the contralateral effect depends on side branches to the right from the actual fibres which go to the left ganglion cells. The view that these branches are indeed a new and recent growth is nearly justified by the consideration of analogous phenomena observed after section of both pelvics (page 426), phenomena that are almost inexplicable unless the possibility of new outgrowths from sound fibres be admitted[1].

Further experiments must decide whether the new contralateral connections of the ganglion cells are weakened and cede to the ipsilateral old, when the latter regenerate to union. In the lapse of 60 days, the longest period as yet allowed, regeneration was found to have occurred, but not to have displaced the old ties.

[1] Lugaro (*Rivista di Patologia nerv. e ment.* XI. p. 327. 1906) has made experiments to examine the possibility of such budding from the medullated fibres of the sciatic nerve, but his results were negative. Perhaps a like outgrowth on the sensory side may explain an otherwise difficult observation by Head (*Brain,* p. 172. 1905). After section of a sensory nerve in man, epicritic sensibility usually takes about a year to return, the time being longer the further the lesion from the periphery. But when the ulnar nerve was severed through about two-thirds of its thickness, epicritic sensibility was regained in three months over all the area innervated by the ulnar.

In brief, after preganglionic section of one motor nerve the decentralised half of the bladder quickly recovered tone: its muscle, remaining very elastic, responded admirably to the hypogastric nerve. The other half of the bladder passed into a state of exaggerated tone, an indication may be of excessive activity of the sacral centres in the spinal cord. Later the surviving nerve obtained control of the paralysed half, and imprinted upon it also the abnormal increase of tone.

The only previous observations regarding these questions are those of Langley and Anderson; that five to ten days after section of one hypogastric in the cat, the other hypogastric had less effect than usual on the sphincter ani (This *Journal*, XVI. p. 426. 1894); that after section of one pelvic nerve the other had less effect on the rectum and the bladder; and that removal of all the sacral nerves lessened the motor power of the hypogastrics on the bladder. Their general deduction was that "section of the nerves appears to lower the irritability of the viscera they supply" (This *Journal*, XIX. p. 382. 1896).

IV. Both pelvic visceral nerves.

The operation is the same as that for section of a single nerve: but the tail should be removed at the same time in order to keep the animal clean. The degeneration removes all the preganglionic sacral motor nerves and nearly if not all the sensory nerves of the bladder.

Disturbance of function. The bladder is then completely paralysed and must be emptied by external pressure on the abdomen. For the first three or four days this action meets with great resistance that seems to lie in deliberate closure of the urethra, for it did not occur in two animals in which the hypogastrics had been cut at the same time as the pelvics. Subsequently the evacuation is performed with great facility. In the third week water in small quantities is voided occasionally, the power of evacuation increasing day by day; and from the sixth week onward there is never further need of attention.

No trouble was ever caused by accumulation of material in the colon. Discharge of fæces, if solid, is very slow and accompanied by eversion of the rectal mucous membrane. The result of this is often a permanent eversion of the last centimetre or so with slight surface bleeding. But usually the material expelled is semi-liquid, its discharge being very frequent and accompanied by that of 10 or 20 c.c. of urine. The micturition is effected unconsciously and without the aid of abdominal pressure, for it was frequently observed while the animal slept. Deliberate application of mechanical pressure generally failed to evoke the discharge; for when the bladder was being emptied by squeezing, it was always necessary to maintain the pressure until the end, as otherwise the outflow ceased though meeting with but little resistance in its passage. Nor was micturition ever produced, as by Goltz in the dog, by inserting a thermometer into the rectum. While generally an incomplete discharge, *e.g.* of 20 c.c. leaving 30 c.c. within, the act was sometimes repeated until the bladder was quite emptied. In these cases of self-sufficiency the bladder was generally of rather small capacity.

Condition of the bladder. The state of the bladder after the injury to its nerves was examined at successive intervals.

On the eighth day, before any power of spontaneous discharge had been acquired, the bladder was relaxed, holding 100 c.c. at a mean pressure of less than 10 cm.; but it exhibited a well marked rhythm. Stimulation of the hypogastrics had a typical result, initial contraction (isometric record) and then fall of intravesical pressure to 5 cm. with arrest of rhythm. Immediately after stimulation the tone was slightly exalted and the rhythm became more rapid. This rhythm was perfectly regular and reacted with uniformity to various stimuli. Thus when the tension was raised by voluminal dilation from 90 to 120 c.c. the beat was

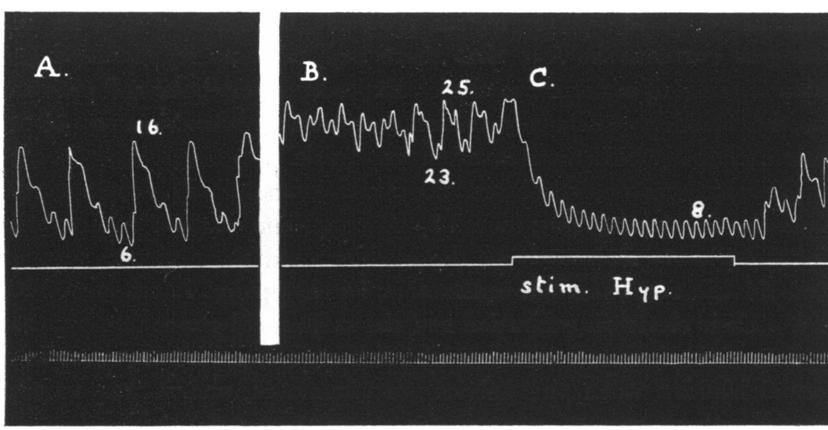


Fig. 15. Rhythmic contractions of cat's bladder on *pressure record* with constant volume. Both pelvics cut eight days previously. A.C.E. Hyp. cut: bladder within abdomen and not exposed.

A. Vol. 90 c.c. waves from 6 to 16 cm., with secondary oscillations due to respiration.

B. Vol. raised to 120 c.c. With the increase of physical tension the crest of each wave attains to 25 cm.; their frequency is increased, and consequently the relaxation between each is less.

C. With same volume stim. hyp., coil 7·5 cm. Slight contraction just as bladder was relaxing from crest of wave: then relaxes to 8 cm. and rhythm vanishes, leaving pure waves of respiration.

accelerated; and relaxation between each wave was brief and incomplete (cp. Fig. 15).

Adrenalin induced very complete relaxation, the bladder being clearly very susceptible of inhibitor influences. General contraction was not seen except as the immediate sequel to the injection of nicotine. After this poison the postganglionic nerves on the side of the bladder produced good local contraction.

So the whole bladder was virtually in the same state as the decentralised half when one pelvic nerve was cut for a like time, being supple and apt for inhibition in contrast with the stiff inelasticity observed after removal of the inhibitor nerves.

No examination was made during the third and fourth weeks when the occasional discharge of urine was commencing.

In the final stage of self-sufficiency for micturition the following abnormality was found on the 46th day after the operation. The bladder was toneless, without rhythm, and enlarged to hold 120 c.c.: the muscular coat was hypertrophied. To avoid reflexes the hypogastrics were cut, and the spinal cord destroyed from the fifth lumbar segment to the coccyx. Stimulation of the pelvic nerves produced no effect even with the strongest current, showing that there had been no regeneration (46 days) of these to motor irritability. Exposure of, or continued pressure on, the bladder occasionally caused automatic contractions of 50 or more c.c., from which the relaxation was quick.

The hypogastrics displayed the most extraordinary sensitiveness. Even the slight stretching caused by placing them on shielded Ludwig electrodes led to their exciting the bladder; and the response was not that of inhibition but a full contraction, for example of 70 c.c. on v. 120, p. 6. Their electrical excitation had the same rapid result (cp. Fig. 16, p. 420). The contraction was of identical character with that seen in a normal bladder when the pelvics are stimulated, and it was equally upheld without relaxation until the stimulus ceased.

On the other hand the injection of adrenalin excited not a trace of contraction of the bladder while it lessened greatly the hypogastric motor action; and in another experiment it was seen that ergotoxine in large doses failed to paralyse the exaggerated motor action of the hypogastrics. The contraction therefore was not being effected by sympathetic postganglionic motor endings of the usual biochemical type; and the abnormality was not to be explained by a direct conversion of inhibitor into motor nerves.

Nicotine was now injected in successive doses of 15, 5, and 10 mgm.

at intervals of about 20 minutes. Each excited the bladder to quick and full contraction, which was followed by as rapid a relaxation and then a steady slow after contraction with development of shallow rhythm. Adrenalin at once inhibited the after contraction. By these successive doses of nicotine the motor effect of the hypogastrics was steadily diminished, and inhibition of the normal type became more apparent. After 15 mgm. these nerves caused on v. 60 a contraction of 9 c.c., a marked drop followed by a pause, and then a contraction of 20 c.c. After the third injection inhibition became dominant, and the result of hypogastric stimulation on v. 80, p. 10 was a contraction of 11 c.c., a long pause, and then relaxation of 22 c.c. (or 11 + 22) with rapid recovery so soon as the stimulus ceased (Fig. 17, p. 420).

This unmasking by nicotine of the normal diphasic action of the hypogastrics suggests that the novel contraction may be attributed to an outgrowth from sympathetic fibres branching in the hypogastric plexus to the decentralised pelvic ganglia, a growth similar to that already assumed to explain the development of the contralateral pelvic contraction. Such endings would not be paralysed by ergotoxine. A little difficulty would occur in the large amount of nicotine that was needed for their paralysis ; but this need was evidently to be referred to the peculiar state of the ganglion cells, as indicated by the fact that they were stimulated by each successive injection of the drug and were not paralysed at once.

A second explanation might, however, be found in the view that the reaction of a muscle to the nervous stimulus does not maintain the same sign at all times in an individual : and that when the tension is uniformly low the muscle may ultimately react to the jar of the nervous impulse by contraction, whereas from a general high level of tension it would be relaxed. So rapid and complete an inversion of response in 46 days is not very probable. Admittedly the tensile conditions accorded in this animal with those needed for the change. But in others the development of the hypogastric motor abnormality was restricted to one side or even to a less area of the bladder : and in these the hypogastric of one side caused inhibition, that of the other full contraction, though the whole bladder was apparently in an equal state of moderately high tone.

Provisionally then it may be assumed that the change was caused by an outgrowth of sympathetic fibres to the pelvic ganglia. The question arises whether these would be from pre- or postganglionic fibres. The paralysis by nicotine refers rather to the pelvic ganglion cells and cannot decide the matter: the failure of ergotoxine to block the impulse only suggests that it was not transmitted through motor postganglionic sympathetic nerves. But the possibilities of crossed regeneration, as defined by the researches of Langley and Anderson, tend to limit the growth to the spinal preganglionic fibres which do occur in the hypogastrics.

Only two experiments directly bearing on this point were made, and their result was unfortunately doubtful. In one the pelvic nerves were cut: 44 days later the spinal cord was excised from the coccygeal up to the 2nd sacral spinal segment so as to prevent regeneration of the pelvics. On the 74th day the abdomen was opened and the hypogastrics tested; the left gave a normal reaction, but the right a fair contraction reaching up to the apex on the right side. The inferior splanchnics were then all cut. Eight days later the hypogastrics were again tried. Excellent inhibition, from 25 to 65 c.c., p. 15, was observed upon their stimulation, but also a large motor effect on the right side. This last was lessened by the injection of nicotine, though it did not disappear.

The second experiment gave no information on the point, for in it 49 days after section of the pelvics the hypogastrics gave only the normal inhibition, and their action was unaltered by six days' degenerative section of the inferior splanchnics.

The last case illustrates another aspect of the abnormal motor action of the sympathetic nerves, namely that it is not necessary for the bladder's recovery from paralysis. In this no further attention had to be paid to the cat after the 42nd day, and yet there had been no change of action of the hypogastric nerves. In another animal the hypogastrics were cut after the natural discharge of the bladder had been established, and the section did not bring back paralysis. Similarly in the two cases quoted above paralysis was not produced by section of the inferior splanchnics. Moreover in two other animals the hypogastrics were cut at the same time as the pelvics, and in these micturition was restored with no delay beyond the usual interval.

From this it is evident that the spontaneous discharge from the bladder, when ultimately established, is a local act that is entirely independent of nerves uniting the organ with the C. N. S.; and that the superadded motor power of the sympathetic described in the first case was an accident and a rarity. Associated with it was an abnormally early recovery from paralysis, the bladder being self-sufficient from the 11th day onward, that is from about the time when, as judged by the period needed for the appearance of the contralateral pelvic effect, the branching nerves could have effected functional union with the pelvic ganglion cells.

If the branches are from preganglionic fibres, then the differing extent to which the abnormal union was found to occur in different individuals may have been determined by differences in position of the ganglion cells on the sympathetic nerves to the bladder, being presumably least when these lie chiefly in the inferior mesenteric ganglia.

The observations recorded above are in harmony with the results obtained by other workers on *dogs*. Mosso, and others subsequently, observed that section of the hypogastrics did not interfere with micturition. Zeissl[1], Lewandowsky and Schulz[2], and Wlasow[3] agree that after section of both hypogastrics and pelvics the bladder eventually developes the power of discharging 100 or more c.c. of urine at a time. Such a development of local activity is similar to that recorded by Goltz and Ewald[4], when the lumbo-sacral cord had been excised. Merzbacher[5] proved the need of sensory impulses for micturition, insomuch as a dog, in which he had cut the posterior sacral and coccygeal spinal roots, could wag its tail at will, but not empty its bladder. But section of the lumbar roots, according to Sherrington[6], paralyses the cat's bladder for only 24 hours.

Müller's[7] results are of interest. After excision of the sacral cord in dogs, paralysis of the bladder gave place in a month or more to unconscious micturition. The bladder wall was then greatly thickened (p. 124). But water was often expelled in fright (p. 117): it was not ascertained whether this was caused simply by abdominal pressure, or by a perverted action of the hypogastrics. In one animal after excision of the cord from the sixth lumbar segment to the end (the segments were not defined by Müller, and are identified conjecturally from his description) reflex erection of the penis could not be produced, but psychical erection did occur. This last disappeared after excision of the lumbar cord as well, and probably must have depended somehow on the hypogastrics. As it was observed within six days of the first operation, it cannot be explained by a new growth of sympathetic fibres with perverted action; and it may have been simply the outcome of central inhibition.

There is then no doubt that the fully decentralised bladder is capable of automatic, if feeble, contraction and discharge of urine. The condition of the bladder, when this power was developed, was the following.

[1] *Wien. klin. Woch.* p. 394. 1896.

[2] *Centralblatt f. Physiol.* p. 433. 1903.

[3] Kasan. 1903. Referred to in *Centralblatt. f. Physiol.* p. 776. 1905.

[4] *Pflüger's Archiv*, LXIII. p. 385. 1896.

[5] *Pflüger's Archiv*, XCII. p. 585. 1902.

[6] This *Journal*, XVII. p. 216. 1894–5. Langley and Anderson (This *Journal*, XVI. p. 431. 1894) stated that section of the first five lumbar spinal roots in the cat paralysed the bladder. The operation should be equivalent to section of the preganglionic inferior splanchnics, which neither in their experiments (p. 427) nor in mine checked micturition. In reality the paralysis was due to injury of the spinal cord, the dissection having crushed and interrupted the path from the brain to the sacral centres. Histological proof of the injury in these operations is recorded in *Proc. Physiol. Soc.* XII. § 2, *ibid.*

[7] *Dtsch. Ztschr. Nervenheilkunde*, XXI. p. 86. 1901.

Histological. The muscular coat was greatly thickened in every layer: its fibres, the histological examination being made with minimal distortion of the tissues by fixing in formalin and cutting frozen in gum, were of greater cross sectional area than those of a normal bladder and they had also increased in number. Strands of new muscle fibres were spread in all directions through the submucosa coat, where they do not normally occur. The hypertrophy was evident in three or four weeks. Changes in the ganglion cells were not determined.

It is not urged that this hypertrophy of the bladder illustrates a general law that plain muscle hypertrophies when decentralised. No change was observed in the colon or urethra. The growth must have been the result of some local causes, probably not a change of blood supply but the mechanical conditions introduced by the paralysis of micturition. Accordingly it did not appear on one side when one pelvic was cut; nor was it seen in two experiments in which the attempt to cut both pelvics had failed of complete success, and a small strand remained to perform a lame micturition.

Physiological. As growth proceeds, the muscle loses the flexibility noticed at the end of the first week, and the capacity of the bladder also is lessened. The power of automatic contraction, that is at last attained, is not associated with a keener sensitiveness of the decentralised muscle and nerve system to any stimuli, except perhaps to those of the temperature changes involved in exposure. Though grown bulkier, the bladder deteriorates in suppleness and irritability. Direct electrical faradisation of its wall causes a contraction that is restricted to an area of 2 or 3 cm. diameter, and does not spread at once over all one side as in a normal bladder. And the contraction is succeeded by a growing contracture. Adrenalin cannot relax the fibre very far; nor does nicotine provoke by excitation of the ganglion cells a full contraction. The stiffness and sluggishness become week by week more marked.

In the longest experiment made, after the pelvics had been cut for 140 days, during the last 70 of which the sacral spinal cord also had been excised to check regeneration, even the automatic contraction of the first months had almost failed and urine simply dripped out. The capacity of the bladder was found to be very small, not yielding to a greater volume than 30 c.c. even when under the influence of adrenalin. The muscle coat was exceedingly thick, and great papillomata projected from the mucous membrane at the apex into the interior. Stimulation of the postganglionic nerves on the side of the bladder caused in their own area a slow but very rigid contraction, from which the relaxation was slow. After 20 mgm. nicotine, neither from these nerves nor from the muscle itself could faradisation elicit a response.

But in one experiment of almost the same duration an opposite result was obtained. Both hypogastrics and pelvics had been cut, and 35 days later the sacral spinal cord was excised. Micturition was unconscious and incomplete; but the bladder was always small and hard to palpation. This was still the case on the 80th day. It was not examined again until the 130th day when it was found to be soft and distended. The animal's brain was then destroyed so that the bladder could be examined without ether. It was found to be moderately hypertrophied but of low tone, v. 100, p. 12. It contracted with exposure, but relaxed at once when returned to the abdomen. Squeezing, so as to raise the intravesical pressure greatly, did not alter the tone; nor did the inhalation of ether. Faradisation of the muscle directly, or of the postganglionic nerve trunks, caused a practically normal reaction without contracture. Nicotine also excited the bladder to full contraction. The pelvic nerves had not, but the hypogastrics had regenerated to both motor and inhibitor effect.

The change in the tone of the bladder between the 80th and the 130th day perhaps was caused by the fresh influences to which the muscle was subjected, as the regenerating inhibitor fibres of the hypogastrics regained touch with them and restored their original elasticity. But there is the difficulty that in the other case quoted, in which the rigidity of the bladder increased progressively up to the 140th day, the muscle was throughout united with these nerves.

Putting aside the later changes in the bladder with the possibility of vicarious contraction by the hypogastrics, and looking only at the state of the muscle in the second five days when the cut old nerves are dead and new fibres have not yet grasped their places, the contrast is clear. Decentralisation of the motor ganglia produces changes the very converse of those sequent to removal of the inhibitors. There is a reciprocal interaction of the two sets of nerves in upholding the muscular "tone." This was lowest when both pelvics were cut and the inhibitor nerves were intact: it was higher, as the succeeding pages will show, when all the nerves and the ganglion cells were taken from the muscle: the increase culminated in the stiff rigidity displayed after section of only the hypogastrics.

V. Denervated muscle.

The muscle was denervated by picking the ganglia off the bladder wall with fine forceps. In all but two cases only one side was so treated, the denervation then being assured by the known fact that each pelvic nerve supplies only its own side of the bladder. During the operation a light clamp was placed on the urethra so as to retain the urine distending the bladder, and ill effects of exposure were lessened as much as possible by covering with warm moist flannels. The hypogastric and pelvic nerves were not revealed; but the branches of the vesical plexus, beginning at the urethra, were torn away and the dissection carefully continued up past one ureter. Pacinian corpuscles as well as ganglia were removed; but probably some of the sacral sensory nerves escaped harm. Especial heed was given to cleaning the large veins, behind the soft wall of which a little ganglion may easily lie hid. Very few of the ganglion cells of the efferent sacral nerves lie buried within the muscular wall, so the denervation was fairly complete[1]. But from these few cells new fibres probably grow, as the weeks pass, out to the isolated muscle, and so progressively diminish the area of denervation.

The operation did not interfere with micturition. Eight experiments of unilateral denervation were made. In each, when the state of the muscle was to be examined, the brain of the animal was destroyed ("pithed[2]"), so as to avoid abnormalities introduced by anæsthetic drugs. The bladder changes were observed under conditions of constant pressure. The reaction to the various nerves was tested and also the direct electrical excitability of the muscle. For the latter purpose faradisation, single induction shocks, and the constant current were tried. In the normal bladder single induction shocks cause a brief and inextensive contraction that may need watching lest it escape notice altogether: faradisation provokes quick contraction of the entire side. A constant current from five Daniell cells in series, when applied to the outer surface by electrodes 1 to 2 cm. apart, does not cause general contraction of the muscle. Though the current be strong enough to liberate bubbles at one electrode, only a slight contraction is seen at the other, and a white

[1] Once the abdominal aorta was clamped for four hours: but this failed to kill the ganglion cells, though it led ultimately to great thickening of the bladder wall.

[2] When only the hemispheres were destroyed by high pithing, the condition developed in the viscera was certainly not that of a general decerebrate atonia. Some visceral reflexes were very prominent. Thus the bowels, which were flushed, whitened with instant vaso-constriction at first exposure to the air. Handling the viscera soon led to repeated reflex vomiting, which was so violent as to hinder examination of the bladder.

Interval after operation	General tone of bladder	Result of stimulating hypogastrics	Result of stimulating pelvics	Result of direct electrical excitation	Result of intra-venous injection of drugs	Remarks
Exp. (i). 7 days	Uniformly high, v. 15, p. 15, lowered only to v. 20 by section of left pelvic.	Right—0 effect. Left—fair + and –.	Right—0 effect. Left—rigid ipsilateral contraction with some contracture.	Faradisation. Right—slow & slight over very small area. Left—very good of all side. Single induction shocks (coil 3). Right—0 effect. Left—good contraction.	Adrenalin, 1 mgm., relaxed to max. vol. of 20 c.c. Nicotine, 10 mgm., contraction only of left side.	Right nerves were completely sundered from right muscle, which had not quite lost electric excitability. Muscle of uninjured side had entered into high tone, and did not relax freely with adrenalin.
Exp. (ii). 8 days	Uniformly high, v. 20, p. 15.	Left—0 effect. Right—fair + and –.	—	Farad. Left—0 effect even with coil at 0. Right—good ipsilateral contraction.	—	Unsatisfactory, was badly pithed, losing blood, and artificial respiration needed. Blood pressure low.
Exp. (iii). 9 days	Moderate, v. 50, p. 15. Contracted with exposure to 20 c.c. but relaxed on left side, when left pelvic cut, asymmetrically to v. 50.	Right—0 effect. Left—0 effect.	Right—0 effect. Left—good ipsilateral with some contracture.	Farad. Right—0 effect even with coil at 2 cm. Left–fair everywhere.	Adrenalin, ·5 mgm., relaxed to v. 60, yielding rather more on right than left. Nicotine, 10 mgm., contraction only of left side.	Firm pinch caused a slight wheal on right side, and no effect on normal left muscle.
Exp. (iv). 10 days	(Little ether before pithing.) v. 40, p. 17. Rt. in rather higher tone. Not lowered by section of left pelvic.	Right—0 effect. Left—fair +.	Right—0 effect. Left—fair of left, with right joining in slowly and feebly.	Farad. good both sides. Constant current (simple and choked): good response everywhere.	Adrenalin, fair – from v. 25 to v. 40 with quick recovery. Nicotine, 10 mgm., good contraction on both sides and equal relaxation.	Pinch, good contraction everywhere, right slightly the better.

Interval after operation	General tone of bladder	Result of stimulating hypogastrics	Result of stimulating pelvics	Result of direct electrical excitation	Result of intravenous injection of drugs	Remarks
Exp. (v). 18 days	Uniformly high, v. 30, p. 15. Left side contracted with exposure to v. 15; returned to v. 30, when left pelvic cut. Very slight rhythm on left side.	Right—0 effect. Left—fair + and −.	Right—0 effect. Left—v. rigid of left and also fair of right. Left postganglionic nerves on side of bladder also caused contraction of right.	Farad. Moderate contraction everywhere, spreading wider on left. Relaxes quickly.	Nicotine, 20 mgm., caused all to contract, left rather better than right: weakened, but did not annul, contralateral effect of left postganglionic nerves.	Was very well pithed.
Exp. (vi). 22 days	(Little ether before pithing.) Tone low, v. 75, p. 15. Not changed by cutting pelvic. Ether, slight contraction from v. 80 to v. 65. Good rhythm on left side, doubtful of right.	Right—0 effect. Left—good + and −.	Right—0 effect. Left—full but purely ipsilateral, with fair relaxation.	Farad. Right—feeble contraction evoked with difficulty, but no contracture. Left—good of all side.	Adrenalin, 0·36 mgm., slowly relaxed from v. 15 to v. 55, right yielding more and for longer time so that bladder was asymmetrical. Nicotine, 10 mgm., right moderate contraction, left rigid.	Pinch, slight contraction everywhere. With exposure right contracted rather more than left, and did not relax after being returned to abdomen for 5 mins.
Exp. (vii). 50 days	V. 40, p. 15, relaxing to v. 50, when left pelvic cut. Slight rhythm.	Right — exaggerated contraction extending up to right apex. Left—normal + and −.	Right—not tested. Left — good of left without contracture and fair of right. Postganglionic nerves, only ipsilateral contraction.	Farad. and single induction shocks, equally excitable everywhere.	Nicotine, 20 mgm., fair contraction of all; abolished contralateral effect of left pelvic and abnormal contraction by right hypogastric.	Regeneration had supplied nerves to right side: right apex was apparently supplied from right hypogastric, and the rest by the left pelvic.
Exp. (viii). 115 days	High, v. 25, p. 15. Not changed by section of left pelvic. Did not contract with exposure. Maximum vol. 40 c.c., yet muscle not hypertrophied.	Right—practically 0 effect. Left—big ipsilateral contraction (+12 c.c.) and fair −. The contraction was a surface crinkling: not lessened by nicotine, but lessened and not simulated by adrenalin.	Right—good ipsilateral with rather slow relaxation. Left—very good ipsilateral and quick relaxation.	Farad. Right rather more excitable than left.	Adrenalin, 1 mgm., pure relaxation but only to v. 40. Nicotine, 20 mgm., full contraction of all, and then preganglionic right pelvic paralysed.	Right pelvic had regenerated with normal cell connections so as to innervate all right side. Perhaps muscle innervated by right hypogastric had actually grown.

In these last two experiments, both sides of the bladder were denervated as well as possible.

Interval after operation	General tone of bladder	Result of stimulating hypogastrics	Result of stimulating pelvics	Result of direct electrical excitation	Result of intra-venous injection of drugs	Remarks
Exp. (ix). 8 days	Toneless, v. 80, p. 10, and without rhythm. Contracted with exposure to v. 50, at which it stood perfectly steady for a long time. Then contracted fully, and from this never relaxed, even with adrenalin, beyond v. 25, p. 20.	Not tried.	Left—0 effect. Right — slight contraction of right base	Farad. irresponsive, except at right base. Constant current, no contraction, only white wheal at anode.	Adrenalin, 0·7 mgm., did not relax beyond v. 25. Nicotine, 10 mgm., no contraction; but temperature of animal had been allowed to fall very low.	Immobility of muscle at various levels of tension was notable. There had never been need to empty the bladder, micturition being incomplete from a constantly large volume. This constant distension, up to 100 c.c., must have tended to numb the muscle.
Exp. (x). 40 days	(Ether anæsthesia). High, v. 20, p. 15, unchanged by section of pelvics. Very slight rhythm.	– 0 effect.	Both together—very small contraction of <5 c.c.	Not tried.	Adrenalin, 0·3 mgm., checked faint rhythm and prevented contraction by pelvics, but did not relax beyond v. 30.	Operation had been followed by small rupture. Bladder was firmly adherent to fibrous tissue filling the gap, and was connected with abdominal muscles which had effected micturition. Bladder wall was greatly thickened.

wheal marks the line of contact of the wire. The result is not altered when the rate of onset of the stimulus is slowed by choking the circuit with the closely wound secondary coil of an inductorium. But even in the apparently normal muscle the response to any stimulus is apt to be lost, when the wall has by retention of urine been long subjected to excessive distension. In only one of the experiments, no. ix, was there reason to fear the introduction of this error.

The experiments made were too few to serve as a safe base for generalisation. They are therefore given in detail in the subjoined table, in order that the value of the deductions from them may be estimated. In each the reactions of the denervated side are named first. There was no manifest change in the blood supply to the denervated side: and as a rule there was but little scarring or adhesion to the peritoneal surfaces.

Cut visceral nerves, according to Langley and Anderson[1], are still excitable in the cat on the 4th day, but have lost all irritability at some date before the 9th day. Perhaps Exp. (i) just touched the dying irritability. In (ii) and (iii) the denervated muscle was numb to the stimulus of electrical faradisation; by adrenalin it was relaxed, but did not contract with nicotine. The muscle of the uninjured side at this time had passed into a state of exalted tone, showing a tendency to contracture. In (iv) and (v) the muscle was almost equally excitable everywhere, and the left pelvic was able to affect the other side of the bladder weakly. It is doubtful to what extent imperfect denervation may be appealed to in explanation of these last two results. But (vi) gave a purely ipsilateral contraction by the pelvic, and a very feeble reaction to electrical and chemical stimuli on the denervated side. The remaining experiments showed return of complete excitability everywhere with regeneration; and also illustrated the compensating spread of the regenerating nerves, by which the few surviving ganglion cells were able to govern all the territory once possessed by many.

From this it seems certain that the quick contraction of all one side, when the normal bladder wall is directly faradised, must be effected by the stimulus spreading in the nerves, not by conduction in the plexus of plain muscle: also that the rhythmic contractions of the bladder are manifested only when the muscle is in connection with its ganglion cells. The denervated muscle contracts where pinched. Doubtful was its irritability toward faradisation. On the whole it would seem that the muscle does respond to the stimulus

[1] This *Journal*, XIX. p. 381. 1896.

and to that of nicotine weakly. From the slight contraction induced by faradisation it relaxes almost as quickly as does normal muscle. The cold of exposure is slow to induce contraction, but the contraction is then abnormally persistent. In Exp. (x) the muscle showed singular immobility at various levels of tension.

Broadly summarising the details of all the experiments, it is seen that the decentralised plain muscle, before entering on the period of torpid overgrowth, is supple and quick to respond in all its area to electrical stimulation, and also exhibits rhythmic movements; but that the denervated muscle has no rhythm, and only dull irritability.

These results must be strictly limited to the bladder. Anderson's[1] experiments on the kitten's heart proved that its rhythm is in no wise dependent on the presence of the motor ganglion cells. Magnus[2] on the other hand found that the rhythmic movements of the cat's intestinal muscle are continually dependent on its union with the intestinal ganglion cells, so as to be lost at once by severance long before the nerve fibres decay.

So, closely considered, the contrast between the physiological capabilities of decentralised and of denervated plain muscle[3] may not be very wide. It is less, the broader the field in which it is examined. And it is a tenable view that of the three nucleated units, the cell in the C.N.S., the cell of the ganglion, and the muscle cell, which are welded to form the efferent chain, any one has an equal native capacity of assuming dominance; hence in the heart the muscle supplies the rhythm, in the intestine and bladder the ganglion cells[4], while for the diaphragm it is those still further back in the respiratory centre[5].

That may well be so, and yet the links of the chain be of very unequal morphological value. The functional value of the ganglion cells seems to be relatively simple. They do not act as peripheral reflex

[1] This *Journal*, XXXI. 1904. *Proc. Physiol. Soc.* p. xxi.

[2] *Pflüger's Archiv*, CII. pp. 123 and 349. 1904.

[3] Cp. Anderson on the sphincter iridis. This *Journal*, XXXIII. p. 156. 1905-6.

[4] The persistence of rhythm in bladder and intestine after the injection of nicotine gives the proof sought by Langley (This *Journal*, XXXIII. p. 400. 1905-6) that the nerve cells retain function after external paralysis by nicotine.

[5] Contrast, too, the dependence of the rhythm of the striped muscle of Limulus' heart on its ganglion cells (Carlson), and the similar dependence of the muscle of Sipunculus' body wall for automaticity on its C.N.S. nerve cells (Magnus, *Archiv f. exp. Path. u. Pharm.* L. p. 86. 1903) with the persistence of rhythm in the denervated muscle of the earthworm as demonstrated by Straub (*Pflüger's Archiv*, LXXIX. p. 379. 1900).

centres, but merely as relay stations on the path of efferent impulses; and in some cases they initiate rhythmic contractions of the muscle. Their removal does not lead to muscular atrophy.

Morphology of the visceral ganglion cells.

The morphological value of the visceral ganglion cells is an unsolved problem of pressing interest. From what tissues are they derived? Is their closest relationship to the central nervous system or to the peripheral muscle? By the presence of these ganglion cells the visceral or autonomic nerves of vertebrates, whether they supply plain muscle or secreting glands, are distinguished from those to the striated skeletal muscles. In gross anatomy the distinction is fundamental. The efferent nerves of both systems issue from the C.N.S. by the anterior spinal roots. But the course of the one nerve to the striated muscle is uninterrupted and direct: that of the other is broken by the ganglion cell. If the ganglion cell is shown to be akin to any structure on the outward course of the skeletal nerves, then the two systems can be homologated with reference to one archetypal plan. Failing that, the cleft between them is profound.

The difference may be lessened by means of the following two assumptions—for their rigid criticism there are not enough data.

1. That the visceral ganglion cells are not emigrants from the C.N.S. or from the spinal ganglia, but are developed peripherally in connection with the unstriated muscle (or other visceral tissue).

2. That the protoplasmic nucleated mass at the nerve ending on a striated muscle fibre is homologous with the visceral ganglion cell connected with unstriated muscle.

The considerations which have inclined me to this belief may be briefly summarised[1].

a. The embryological evidence upon the origin of the visceral ganglia is equivocal.

b. Physiologically there is no kinship between the spinal root ganglion cells and those of the visceral ganglia. The former are on the course of sensory afferent, the latter on efferent fibres. Nicotine and curare do not affect the one, they block the passage of impulses outwards through the other[2].

c. Tested biochemically by their reactions to nicotine and curare,

[1] The argument has previously been outlined in a communication to the Physiological Society, Dec. 16, 1905. This *Journal*, XXXIII.

[2] Langley. This *Journal*, XXVII. p. 224. 1901.

the visceral ganglion cells must be classed with the "motor plates" on striated muscle.

Nicotine stimulates and then paralyses the ganglion cells of all visceral nerves[1]. In slightly larger doses it paralyses the nerves to striated muscle; and it was shown by Langley to stimulate certain striated muscles in the bird and frog. Both in striated muscle and in ganglion cells of unstriated the stimulation can occur after degenerative section of the efferent nerves from the C.N.S. Langley[2] concluded from this that nicotine in stimulation affects the muscle ("receptive") substance directly. But it may rather be that the action of the poison is still localised on the nervous side, though beyond the nerve branching. The common points for the two tissues would then be the motor plate of striated, the ganglion cell of unstriated muscle.

Similarly curare paralyses the "motor nerve endings" of striated muscle in vertebrates; and in larger doses paralyses the visceral ganglion cells[3].

d. Taking next the possibilities of crossed regeneration of nerves Langley and Anderson[4] have shown that any preganglionic visceral fibre can supplant the motor nerves to striated muscle, and *vice versa*; but that in the visceral class preganglionic fibres cannot unite with unstriated muscle except through the intermediary of a visceral ganglion cell[5]. In other words, all the primary efferent nerves leaving the C.N.S. are of one class. All can unite with a visceral ganglion cell, but only thus indirectly with unstriated muscle: all can unite "directly" with striated muscle. The facility of cross union indicates a similarity in nervous structure between the ganglion cell and the protoplasmic mass of the motor plate.

e. The rhythmic contractions and the faradic excitability of the cat's bladder depend largely on the connection of the muscle with its ganglion cells. Skeletal striated muscle has been so subordinated to the initiative of the C.N.S. that it atrophies to meagre tenuity after section of its nerves, and the atrophy conceals possible physiological activities[6]. But

[1] The broad rule includes various discrepancies noticed by Langley in his general criticism of the value of poisons as means of morphological analysis. This *Journal*, XXXIII. p. 408. 1905–6.

[2] *Ibid.* p. 399. [3] Langley and Anderson. This *Journal*, XIX. p. 139. 1895–6.

[4] This *Journal*, XXXI. p. 365. 1904.

[5] A possible exception is discussed by Anderson, *ibid.* XXXIII. p. 434. 1905–6.

[6] Loss of faradic irritability by degeneration of the nerves to striated muscle is not universally the rule. In the cat (Sherrington. This *Journal*, XVII. p. 253. 1894) the muscle of the body at no time exhibits such loss.

one striated muscle, the external sphincter ani[1], is less dependent on the C.N.S. It does not dwindle after section of its motor nerves, but soon regains a little tone, exhibits rhythmic contractions and a very sensitive irritability toward faradisation. The faradic stimulus then in general may be affecting not the muscle but something of a nervous nature[2] that survives at and beyond the "motor plate" in the muscle mass. The same nervous "postganglionic[3]" network would, upon the view of the action of curare which I have detailed above, receive the faradic stimulus when the motor nerves have been paralysed by this poison.

f. The developmental relationship of the muscles to the nerves. In monsters born without a C.N.S. the striated muscles may be developed perfectly[4]. In such an amyelous fetus dissected by Sherrington[5] the motor nerves to the striated muscles were altogether absent. The ganglia and only the postganglionic nerves of the visceral systems with their muscles were present. So here by common default, as above by common action, the motor nerves to striated muscle are classified with the preganglionic visceral nerves. Unfortunately no histological observations record the condition of the motor plate in such monsters[6].

g. Striated muscle is undoubtedly the oldest of the contractile tissues in the vertebrate body, just as it is the only muscle of the Arthropods. Its development has been continuous; and in almost all animals there is found a nucleate mass of protoplasm as intermediary

[1] So Goltz and Ewald, Merzbacher, Müller, and Fuld. In some rats from which I had removed the lumbo-sacral cord (This *Journal*, XXXI. p. 287. 1904) the tone of the sphincter ani was good: but it was always lax in my cats. In the latter animals the muscle did not react to stretching; but it was very readily irritated by faradisation, and the contraction then spread at once over all the muscle including, oddly, its prolongation around the vagina.

[2] Cp. Keith Lucas. This *Journal*, xxxv. p. 103. 1906–7.

[3] By the use of curare it has been calculated that there is a delay of ·005 seconds in the motor plate. This is practically the same as that calculated for transmission through a cell synapse in the C.N.S. The corresponding time values for plain muscle and its nerves have never been determined.

Judging from the behaviour of the electrical organ of Malapterurus, on which nicotine has not been tried, it would seem that curare does not hinder the development of the E.M.F. changes where the excitatory impulse meets the nervous tissue at the primary synapse. And for this response there is no loss of time in the nerve ending.

[4] A number of such cases are cited by Neumann, *Arch. f. Entwickelungsmechanik*, XIII. p. 448. 1902: but none had been analysed so fully as that by Sherrington.

[5] This *Journal*, XVII. p. 250. 1894.

[6] Deliberate interference with embryonic development has not to my knowledge touched the question from this point of view. Granville Harrison (*American Journ. Anat.* III. p. 216. 1904) concludes from experiments on the frog that the motor nerves usually innervating striated muscle play no part in its morphogenesis.

between the motor nerve and the muscle. This mass, the "sole of the motor plate," is presumably developed from the protoplasmic "neural" half of such an original unit as the Hydra's myo-epithelial cell.

Unstriated or plain muscle of the vertebrates is a tissue totally unlike that of the lower groups: its cells are small, the efferent nerves to it are ganglionated. Its origin, whether as an entirely new formation or by remodelling of some older type, is unknown. But the homology that I have suggested would recognise in the ganglion cell the same "neural" half of the myo-epithelial unit as that which has made the cone of Doyère or the "sole[1]" for the striated muscle. The efferent fibres from the proper nervous system have in each case become united with the same part.

It is to be noted that the cranial and sacral visceral ganglion cells lie quite close to the peripheral muscle: and as the functions subserved by these great groups of plain muscle and nerve, namely those of ingestion of food at the oral end and of its excretion at the other, are of the earliest need, it may be supposed that they present the archetypal form, a further reason for believing the position of the ganglion cell to be originally peripheral. The contractile material, and especially that of the sympathetic subdivision, has been dragged away in the walls of the various organs, become endowed with nuclei of its own, and multiplied to form muscle sheets. It is even possible that the unstriated muscle of the gut has again budded forth nervous material, and so made the local connections of the intestinal ganglia[2] as an offshoot not directly connected with the spinal nerves.

This hypothesis does not conflict with the arguments that I have used for the recognition of the "myoneural junction[3]" where peripheral nerve meets muscle. My conception of this was, so to speak, purely biological, attempting no further objective analysis. Sherrington's[4] physical picture of a "synaptic membrane" may be applicable. But

[1] Cp. Kühne's figures from cat's muscle, with an almost diagrammatic ending of each branch of the motor axon upon a nucleus of the motor plate (*Ztschr. f. Biol.* XXIII. Fig. 317. 1887). A serious difficulty is presented by the absence of any obvious protoplasmic mass in the nerve endings of certain amphibia. The nuclei of Kühne's "Endknospe" may represent this: but they lie on the nerve fibres, and not between them and the muscle.

[2] The intestinal plexuses in the bird appear latest of all, and the masses of the ganglia are formed chiefly by local multiplication. W. His, junr. *Arch. f. Anat. u. Physiol. Anat. Suppl.* p. 137. 1897.

[3] This *Journal*, XXXII. p. 436. 1905.

[4] This *Journal*, XXXIV. p. 37. 1906.

Langley's[1] identification of it with a chemical "receptive substance" is not easily adapted to the facts of the innervation of the bladder. He believes that a receptive substance for the nervous impulse, a substance which may be identical with that for chemical stimuli such as adrenalin, is differentiated in the protoplasm of the peripheral reacting cell. The substance appears in process of time through the latent tendency of the cytoplasm to chemical variation (by definite mutation ?) independently of the union attempted by the nerve. Failing this substance an entrant nerve cannot effect functional union with a cell. Chemical variation must, therefore, be synchronous and similar over an extensive area, for example in all that of the sympathetic muscle, which displays a common class of reactions to stimuli.

Langley's view explains admirably the persistence of a given excitability in the peripheral cell after degenerative section of its nerve. But it does not clearly ascribe a determinant value to the entering nerve, which must knock patiently unheard until the cell chances to develope the proper receptive substance. I gave a definite value to the play of the nervous impulse, so that the union, whether pre-existent or acquired, should soon evoke in the cytoplasm of that cell machinery reacting to a given chemical or nervous stimulus, machinery which was not in existence before.

Strictly interpreted, the "receptive substance" theory is a doctrine of inflexibility. Upon it nervous union can do nothing to effect a particular nervous control until the sudden variation of the peripheral substance shall arise and introduce the action. The explanation suggested by Langley of the main discrepancies between the action of adrenalin and that of the sympathetic nerves runs at once into this obstacle. Pilomotors of the skin and the dilator muscle of the iris are in some animals much less responsive to adrenalin than are the muscles of deeper visceral structures. Langley suggests that this difference may have origin in the fact that these peripheral structures were developed at different phylogenetic epochs. Yet instances occur where these skin structures or the dilator pupillæ are most sensitive to adrenalin; and these are instances where the tissue is worked daily and hourly by the nervous system, where the nervous action does seem to have engendered the particular irritability.

The difference between the two theories may be fairly tested by applying each to the case of the cat's bladder. In most mammals the

[1] This *Journal*, XXXIII. p. 374. 1905–6 : and Croonian Lecture, *Proc. Roy. Soc.*, Series B., LXXVIII. p. 193. 1906.

main element of the bladder wall is a sheet of plain muscle which contracts in response to stimulation of the sacral nerves, and which is indifferent to adrenalin and to stimulation of the sympathetic nerves. Therefore on Langley's view its muscle cells contain a receptive substance for sacral nervous impulses, and for these alone. In the cat, and in some other animals, this identical muscle is inhibited by adrenalin and by the sympathetic nervous impulses. Chemical variation in the muscle must therefore have occurred and given birth to the proper receptive substance which the waiting nerve might seize. But such chemical variation would hardly be expected to occur sporadically in different members of a zoological genus, as is the case with this peculiar form of double innervation. Still less probable would be its failure to appear in the abnormal examples that I have cited (p. 377), where the bladder muscle existed but not the sympathetic nerves, and where the muscle could not be inhibited by adrenalin.

The question has more than an academic interest of definition. Recent workers are agreed that the peculiar reactions of various tissues do not inhere immediately in the "nerve endings," if these be defined as the microscopically visible terminations of the axons. Viewing the debatable land beyond the nerve ending, Langley attains to a generalised conception of the receptive substance which differs fundamentally from the idea that I have tried to present. To attribute all change to independent chemical variation in a peripheral cell and to deny all power of the nerve to engender a particular irritability in a tissue with which it seeks connection, whether continuity or discontinuity be accepted, is a theory of precision but of such rigidity as to make difficult a comprehension of the flexible yet orderly co-ordination of all nervous activities. Further it almost disallows the method which I have tried in the preceding pages to use for tracing with biochemical tests the steps of morphological evolution.

SUMMARY.

The chief points of this paper are:—

1. The physiological innervation of the bladder differs from animal to animal, even as its anatomy does.

2. In all mammals the pelvic visceral or sacral nerves cause the whole bladder to contract: in the cat and rabbit, and probably in others, they also inhibit the sphincter. Hence the pelvic visceral nerves (nervi erigentes) are the nerves of micturition.

3. The cells of the spinal cord which give origin to these nerves lie in the sacral segments below the lumbar enlargement. This lower segment of the cord is sufficient for reflex micturition.

4. In the cat the hypogastric nerves, whose root origin is above the lumbar enlargement, constrict (but do not shorten) all the urethra and relax the bladder. They are the nerves which facilitate retention of urine.

5. The cell relays of these inhibitor nerves in the hypogastrics lie chiefly in the inferior mesenteric ganglia side by side with those of the motor nerves to the urethra and base of the bladder.

6. Inhibition by the hypogastrics is seen to a less degree in the monkey and apparently in the pig: there is no good proof of its occurrence in man.

7. Automatic rhythmic contractions practically do not occur in other bladders than those which possess inhibitor nerves.

8. In the dog the hypogastrics control only a very small area at the base of the bladder close to the sphincter, and in this they produce only contraction as they do in the cat: synchronous and universal inhibition of the rest of the bladder, as seen in the cat, is not produced.

9. Similiarly in the rabbit, female goat, mongoose, etc., the hypogastrics innervate only a narrow area at the back of the bladder.

10. But in the ferret conspicuously, and to a less extent in the male goat, the contraction evoked by the hypogastrics includes the whole bladder. Perhaps the muscle innervated by the hypogastrics is here a sheet separate from that innervated by the pelvics, being an upward extension from the area between the ureters where contraction is observed in all mammals. Its functional use was not ascertained.

11. Constriction of the ureters is not caused either by stimulation of the sympathetic nerves or by the application of adrenalin.

12. The cat's bladder is both by its anatomy and by its innervation peculiarly specialised for the storage of large quantities of water. The presence of inhibitor nerves is a chief part of this specialisation.

13. Degenerative section of the inhibitor nerves to the cat's bladder heightens its tone. The bladder becomes of smaller capacity, its muscle fibres are less supple, and it loses much of its automatic rhythm: that is, the muscle assumes properties similar to those exhibited in animals whose bladders have never possessed inhibitor nerves.

14. Degenerative section of one pelvic nerve is soon recovered from. The decentralised side regains tone: and within three weeks it is found to contract perfectly well in response to stimulation of the surviving

contralateral pelvic nerve. Early before this novel control has been established, the paralysed muscle is in the best condition for the demonstration of inhibition by the hypogastric nerve.

15. Section of both pelvic nerves lowers the tone of the muscle, leaving, however, its spontaneous rhythm. Micturition is paralysed. Four or five weeks later the bladder developes the power of spontaneously discharging some of its contents. This power is not altered by section of the hypogastric nerves or by excision of the lumbo-sacral spinal cord: it is a local, though lame, reaction.

16. Earlier and better recovery from the paralysis may in some cases be attained by the hypogastrics. These inhibitor nerves then become motor. The change is not an essential inversion of the function of the original nerves, but seems to be due to an outgrowth of fibres from the hypogastrics to the isolated ganglion cells of the pelvic nerves.

17. It would appear by the results of 14 and 17 that from quite uninjured nerve fibres side branches may bud out to unite with decentralised ganglion cells.

18. Direct faradisation excites the muscle of the cat's bladder indirectly through its nerves. Complete denervation of the muscle depresses its electrical excitability.

19. It is suggested that the nucleate protoplasmic mass of the motor nerve ending in striated muscle and the visceral ganglion cells of the nerves to plain muscle are homologous, and further that the visceral ganglion cells in vertebrates are not derived from the central nervous system but are of peripheral origin.