THE PERIPHERAL SYMPATHETIC INNERVATION OF THE UTERUS.

By

AMY MARGARET FLEMING, B.Sc., M.B., Ch.B.

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CONTENTS.

I.

The present investigation was undertaken to throw some light upon the nature and mode of action of the peripheral nervous mechanism of the uterus.

Previous work has demonstrated that the organ, like other viscera, has an autonomic action. It has been proved both clinically and experimentally that the uterus and vagina can function independently of the central nervous system.

Sir J. Y. Simpson[1] working on the pig showed that spontaneous birth could occur after destruction of the lumbar and dorsal regions of the cord.

Goltz[2] observed conception and spontaneous birth in a dog after section of the cord at the level of the first lumbar segment.

Riemann[3] observed spontaneous birth in a cat after destruction of the cord from the third dorsal segment downwards.

Rein[4] showed that even after section of the nerves to the uterus and removal of the cervical ganglia in a pregnant dog, the litter was born.

Kabierske-Heidenhain[5] and Masius[6] showed that even after time had been allowed for degeneration after section of the nerves to the uterus normal birth occurred in dogs.

Kurdinowsky[7] showed that birth occurred from a rabbit's uterus extirpated late in pregnancy.

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II.

The nervous mechanism of the uterus may be divided into a central and a peripheral part.

A. Central Part.

(1) Cord:- The existence of a centre in the lumbar region of the cord according to Langley and Anderson[8] was shown by the experiments of Valentin Bracket, Longet and Budge.[9]

(2) Splanchnic Nerves:- The fibres destined for the uterus and vagina pass chiefly by way of the sympathetic in the region of the 4th, 5th and 6th lumbar ganglia.[10] In the cat and rabbit[8] it was shown that stimulation of the 2nd, 3rd, 4th and 5th lumbar nerves caused pallor and contraction of the Fallopian tubes, uterus and vagina.

(3) Inferior Mesenteric ganglion:- Langley and Anderson[11] have shown that a variable number of the preganglionic nerve fibres to the uterus form cell stations in the inferior mesenteric ganglia, that many run on to the peripheral nerve cells on the hypogastric nerves and that occasionally all pass through the inferior mesenteric ganglia to join the more peripheral nerve cells.

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(4) Hypogastric nerves:- From the inferior mesenteric ganglia the nerve fibres pass down the aortic plexus to the region of the bifurcation of the aorta. There they separate to form the two hypogastric nerves. They form the hypogastric plexus within the pelvis from which fibres pass to the rectum, internal genital organs and bladder.

(5) Pelvic nerves. The hypogastric plexus receive branches from the sacral nerves (Langley and Anderson)[11] chiefly from the third and fourth sacral.

Fellner[12] reports that V. Basch and Hoffmann[13] observed shortening of the body and drawing in of the cervix and contraction of the external os to follow stimulation of the pelvic nerves. Fellner himself obtained in the uterus of the dog, upon stimulation of the nervi erigentes, contraction of the longitudinal and relaxation of the circular muscle of the body of the uterus and contraction of the circular and relaxation of the longitudinal muscle of the cervix.

Langley and Anderson[8] however, in the cat and the rabbit, and Dale and Laidlaw,[14] (1912) in the guineapig, failed to obtain any effect on the uterus by stimulation of the nervi erigentes.

Gaskell[15] considered it has been shown conclusively that both motor and inhibitory fibres for the musculature of the uterus/

uterus arise from nerve cells belonging to the lumbar outflow, there being no evidence that they are connected with the pelvic nerve.

B. Peripheral Part.

(1) Cervical Plexus or Ganglion.

The position and relations of the peripheral cell stations and their morphology are imperfectly known. Langley and Anderson[16] describe in the cat groups of ganglionic cells in the hypogastric nerve near the cervix and in the rabbit similar cell stations at the dorso-lateral border of the vagina. From these they find a ganglionated plexus stretching along the vagina. Holste[17] found groups of ganglionic cells in the connective tissue at the level of the cervix in the guineapig.

Körner[18] as early as 1863, and Polle[19] in 1865 are reported by Labhardt[20] to have discovered in the human subject ganglionic cells in the connective tissue around the upper half of the vagina and the cervix. Lee,[21] Frankenhäuser,[22] Hashimoto[23] and Jung,[24] all described a large cervical ganglion lateral to the uterus, whereas Pissemski[25] found ganglia scattered along the branches of the hypogastric plexus at both sides of the cervix. Recently Mabuchi[26] has confirmed this, describing 2 lateral, 2 ventral and a dorsal ganglion at the level of the cervix.

(2) Intra muscular nerves.

According to Labhardt,[20] Kilian,[27] (1851) was the first to demonstrate nerves within the uterine wall of lower animals and man/

man. Frankenhäuser[22] traced single nerve fibres to the mucous membrane. Gawronsky,[28] working on the human subject, the guineapig, mouse, sheep and dog (Golgi's method) described the nerves within the muscle of the uterus as running in thick bundles, dividing into very fine fascicles under the mucous membrane running parallel to its surface and thence sending out vertically into the mucous membrane very fine branches which end in knobs. Labhardt[20] and Mabuchi[26] however failed to detect any nerve elements in the mucous membrane of the uterus.

The mode of ending of the nerve fibres within the muscle is still unknown. Koestlin[29] described minute fibrils ending free or in knobs in the rabbit (Golgi). Labhardt,[20] however, in man showed the nerve fibrils in the muscle sheath to end sharply with no knobs. In places he could see an intensely blue coloured pointed ending (methylene blue). Mabuchi[26] described small spindle-shaped endings. All three agree that the nerve fibrils are not sufficiently numerous to allow each muscle cell to be supplied by one nerve fibril.

Opinion is divided on the question of the existence of nerve cells on the nerves within the uterine wall. Much work has been done using all the common special nerve stains. According to Mabuchi[26] other workers such as Polle,[19] Henle,[30] Lüschka,[31] Hashimoto,[23] Jung,[24] Krause[32] and J. Ogata[33] describe nerve cells only outside the uterine wall.

Körner[18]

Körner,[18] Mezincescu,[34] Röhrig,[35] Rein,[4] and Dahl[36] failed to find ganglionic cells within the wall, although Dahl reports that Oudenal[37] found small ones in the uterus. On the other hand Gawronsky[28] described cells in the uterine parenchyma such as had been found by Patenko,[38] Schenk,[39] and Herff,[40] and considered them to be nerve cells. In the case of the cells resembling nerve cells found by Clivio,[41] Köstlin,[29] Hoogkamer,[42] Spiegelberg,[43] Spampani,[44] and Mabuchi[26] within the uterine muscle, their nature was not proved as their connection with nerve fibres was not made clear. Keiffer[45] (Cajal's method) reports the presence of small ganglionic cells within the uterine wall of the cat and guinea-pig. S. Ogata[46] failed to find in the rabbit the ganglionic cells described by Brill (47) (Cajal's method).

It is with the peripheral part (B) of the nervous mechanism of the uterus that the present investigation is concerned.

In all viscera this is formed by the emigration of Neuroblasts from the embryonic spinal cord and these remain in synaptic connection with augmentor and inhibitory neurones in the cord. (Onodi,[48] Kuntz,[49] and Abel.[50]).

<u>The physiology of the peripheral ganglia of other organs</u>.

Much work has been done upon the physiology of the great/

great myenteric plexus in the walls of the alimentary canal (Bayliss and Starling,[51] Magnus,[52] Cannon[53]) and its importance in the autonomic control of the movements of the digestive canal is recognised. It is something more than a mere cell station on the efferent visceral nerves.

The plexuses in the heart wall are very generally regarded as mere cell stations on the inhibitory fibres of the vagus. But the results obtained by Letters[54] strongly suggest that they too, at least in the frog, have an autonomic action in controlling the rate of the heart.

The work of Sokowin[55] on the influence of the inferior mesenteric ganglia on contractions of the bladder suggests that a peripheral reflex mechanism may exist there. The possibility of a true reflex existing cannot be ignored, even although the work of Langley and Anderson[16] (1894) has led to the conclusion that this is probably an antedromal effect.

The work of Meltzer, Auer and Githens[56 & 57] on the iris in the cat and rabbit points to the superior cervical ganglion being more than a mere cell station. The presence of a marked dilatation with adrenalin only after denervation Anderson[58] and Elliott[59] attribute to an increase of excitability of the contractile tissue. Pollock[60] found that the mydriasis produced by hypophysin was increased by decentralisation and still

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more by deganglionation of the dilator pupillae.

Little is known about the function of the peripheral nervous mechanism of the uterus. Keilmann,[61] Knüpffer[62] and Weidenbaum[63] merely conjectured from the anatomical relations of the parts during pregnancy and labour that the pressure of the child on the groups of ganglionic cells near the cervix had an influence on the progress of labour.

Köstlin,[29] Labhardt[20] and Mabuchi[26] agree that sufficient nerve fibrils do not exist to allow each muscle cell to be supplied by one nerve fibre. They conclude that stimulation must pass directly from muscle cell to muscle cell as in the ureter (Engelmann).[64]

The terminal neurones may be of the nature of the common efferent path of the outgoing neurones to skeletal muscle, Fig. 1 A functioning differently according to the nature of the impulse reaching them, or they may be of two kinds, one augmentor and one inhibitory, each having independent endings in the muscle fibres either acting upon a common receptor substance, Fig. 1 B or each provided with a special receptor substance, Fig. 1 C between the nerve ending and the contractile substance.

It has been very generally accepted that on the course of the visceral fibres there is only one synaptic interruption or cell station. The evidence for this is by no means conclusive and/

and in one of his most recent papers Langley (65) admitted that more than one cell station may exist on the nerves of the intestine. Thus there may be a cell station in the inferior mesenteric ganglion and another in the cervical ganglion or intramuscular ganglionic structures, if such exist.

III. ANATOMY.

While Langley and Anderson gave a detailed description of the nerves of the pelvis of the cat and the rabbit, so far the arrangement of these in the rat, guineapig and mouse has not been investigated. Their arrangement in the human subject also deserves fuller treatment than it has yet received.

In Fig.II and III the course of the inferior mesenteric plexus and the hypogastric nerves (H.N.) is shown in the rat and guineapig respectively. The hypogastric nerves pass distally in close relationship to the ureter (Ur) and then towards the uterine wall along with the uterine artery (U.A.).

In Fig. IV is shown a dissection of the branches of the hypogastric plexus of the guineapig and its connections with the 2nd and 3rd sacral nerves (Sii and Siii). Histological examination confirmed the fact that these strands contain nerve fibres.

Complete serial sections of the genital tract of the rat, guineapig and mouse were prepared to locate the positions of the peripheral ganglionic cells in or near the uterus. The vertebral column and pelvic bones were dissected out and the pelvic contents embedded in paraffin. In the rat serial longitudinal and in guineapig and mouse serial transverse sections were then prepared each 10 microns thick.

A few sections were in each series stained with haematoxylin/

haematoxylin and eosin and the remainder were prepared by a modification of the methyl-green-pyronin method used by Hyrntschak.(66) With this special stain the best results were obtained when the staining in methyl-green-pyronin was continued between 2 and 3 hours at 37°C. No better results were obtained by increasing the proportion of pyronin from 0.3% to 0.6%. The sections were very rapidly dehydrated and cleared in acetone, absolute alcohol and xylol.

This stain gives the protoplasm of nerve cells a very bright red granular appearance which is conspicuous beside the faintly stained wall of the uterus. Each nerve cell contains a light blue nucleus with a red violet nucleolus. Nerve fibres stain less deeply than do the smooth muscle fibres of the uterus, bladder and rectum, and the cells forming the coats of the capillary vessels. Bundles of nerve fibres in cross-section appear almost unstained and of a glistening appearance.

For each animal a reconstruction has been made with the aid of the glass plate method giving the distribution of the branches of the hypogastric nerves and showing the position of groups of nerve cells on their course. A brief report of each is of interest here.

1. RAT.

A. The Cervical Ganglion.

In a new-born rat ganglionic tissue had been demonstrated by Watson in the Physiological laboratory, Glasgow University, on each side in close contact with the muscle of the lower part of the cervix (c). Fig.V.

The reconstruction Fig.VI shows that in the adult rat a large cervical ganglion is present surrounding one of the main branches of the uterine artery (U.A.) and lying within 0.2 mm. (in this rat) from the lateral wall of the cervix (c). Besides this large ganglion scattered groups of cells occur on those portions of the branches of the hypogastric plexus opposite the vagina (V) and the part of the uterus distal to the separation of the two horns (H.U.).

B. Intramuscular Nerve Cells.

Portions of uterine wall were stained by the Intra-vital Methylene-blue method, but no nerve cells were found.

No cells having the typical stain and morphology of the nerve cells in the cervical ganglion were found within the uterine muscle, although haematoxylin and eosin, methyl-green pyronin and several modifications of Nissl staining were employed. In each case the staining was controlled by simultaneous staining of sections of the intestine of the rat. In these control sections nerve cells were clearly shown in the intestinal wall.

2. GUINEAPIG.

A. Cervical Ganglion.

Attempts were made to locate the position of the peripheral nerve cells on the branches of the hypogastric plexus outside the uterine wall in the adult guineapig. It was found impracticable to prepare serial sections of a block large enough to include the relatively large uterus and sufficient width of the broad ligament to include the cervical gangion. For the reconstructions Figs. VII, VIII, IX, therefore, a female foetal guineapig of about 60 days' development was used. The 2410 transverse sections are numbered commencing from the lower end of the tract (from the vagina proximally).

On the hypogastric nerve (H.N.) ganglionic cells are scattered but are most numerous on that part distal to the level of the junction of the horns (Figs.VIII and IX). From this latter part arise the ganglionated branches supplying the uterus, rectum (r), and bladder (b). As in the rat no ganglionic cells were found on those parts of their course opposite that part of the uterus proximal to the level of the junction of the horns.

The cervical ganglion is less circumscribed than in the rat and lies close to the uterine artery (U.A.) lateral to the wall of the cervix (c) at this stage of development. As the course of the nerves and arteries cannot be recorded from glass plate reconstruction, without to some extent projecting them on to the topmost of the series of sections, a graphical reconstruction Fig. X was also made. Fig. X. shows the

nerves and arteries passing to the uterus, cervix, and vagina (v).

B. Intramuscular Nerve Cells and Fibres.

In the above series of sections, in which the nerve cells within the wall of the intestine and bladder were shown up with the methyl-green-pyronin staining, there were no similar cells seen within the uterine wall. The contrast is very striking, because on each slide a section is seen of the entire pelvic contents.

No typical nerve cells were found in three series of longitudinal sections of the uterus of new-born guineapigs stained with haematoxylin and eosin, by Nissl's stain and by Cajal's method respectively.

Portions of the uterus and of the small intestine of the guineapig were stained simultaneously by Cajal's and others by Bielschowsky's method. Nerve cells and non-medullated nerve fibres were identified in the intestinal wall; but although non-medullated nerve fibres were seen in the uterine wall, no nerve cells were found.

3. MOUSE.

A. The Cervical Ganglion.

No dissections of the hypogastric nerves were made in the mouse because in a mouse about one week old the sympathetic nerves to the uterus could be traced in transverse sections from the inferior mesenteric ganglion. In this series the 684 sections are numbered, commencing from the vaginal end. From the aortic plexus lying first anterior to the inferior vena cava and then anterior to the aorta a ganglionated nerve plexus passes to the intestine along with the tortuous inferior mesenteric artery. Just distal to the bifurcation of the aorta the aortic plexus divides into the hypogastric nerves which pass downwards and forwards on either side of the rectum (R). The hypogastric nerve begins to divide to form the hypogastric plexus 1 cm. below the level at which the horns unite, i.e., at the same level at which the cavities of the horn fuse to form one. Nerve cells occur on the course of the branches of the hypogastric plexus.(Fig.XI). The nerve cells are especially numerous lateral to the vaginal fornix (V). Here the plexus intertwines with the vaginal branches of the uterine artery (U.A.) and sends divisions anterior and posterior to the vaginal fornices. In Fig. XI the anterior ganglionated strand is seen to pass mainly to the bladder (B) but ganglionated branches also pass to the adjacent vaginal wall. On the branches of the anterior division, ganglionic cells cease to be numerous distal/

distal to the upper end of the urethra.

The posterior ganglionated division gives off branches accompanying the arteries running down the postero-lateral surface of the vagina. A distinct cervical ganglion is not seen in the mouse; instead there is a ganglionated plexus lying within 0.02 cm. of the vaginal fornix.

B. Intra-muscular Nerve Cells.

Although sections in which both intestine and bladder were mounted along with the uterus showed the presence within the intestinal and bladder wall of nerve cells staining characteristically with either methyl-green-pyronin or Nissl's stain; no nerve cells were seen in the uterine wall.

Portions of the horn of a pregnant mouse, almost at full time, were stained by various modifications of Cajal's method including that of Ranson, and also by Donaggio's method. No nerve cells however were found.

Certain bodies somewhat resembling nerve cells were found in the uterine wall of these three animals. These cells showed greater affinity for the silver staining than did the surrounding connective tissue and muscle. Some of these cells had an irregular outline, this on occasion being sufficiently marked to regard the cells as having blunt processes. The idea that these were nerve cells would not have/

have been entertained had it not been that in some instances in addition to the blunt processes mentioned a fibre of some length and impregnating with silver was seen. So far by Bielschowsky's method I have been unable to decide whether these are nerve cells or specialised connective tissue cells. Further work is required on this question before it may be considered as clearly settled.*

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* At present I am endeavouring to arrive at a modification of Bielschowsky's method in which an impregnation of the connective tissue and muscle is completely avoided and yet a successful impregnation of the nervous tissue obtained. Agduhr[67] has shown that the degree to which the connective tissue is impregnated depends amongst other factors upon the proportion of sodium hydrate in the ammoniacal silver solution. An increase in its amount increases the staining of the connective tissue. Yet upon decreasing the proportion there is an increased tendency for the silver deposit to be removed during treatment with xylol preparatory to embedding in paraffin. Agduhr however in contrast to Mabuchi[26] considers that by suitable treatment with a dilute solution of acetic acid a point may be reached at which the acetic acid has completely prevented the reduction of the silver in the muscle and connective tissue and yet not in the nerve tissue. I am carrying out a series of experiments with a view to settling (1) the correct proportion of sodium hydrate in the ammoniacal silver solution for the impregnation of the nervous tissue in uterine muscle and (2) upon the duration and concentration of the weak acetic acid bath and (3) upon the duration of toning with dilute gold chloride.

4. HUMAN SUBJECT.

In the Human as in the guineapig, it is not possible to prepare complete serial sections of a block large enough to include the adult uterus and cervical ganglion, therefore an investigation was made upon a female foetus of about 4 months' development, which appeared to be normal. As Ogata (33) has shown that nerve cells had developed in the connective tissue outside the uterus, even in a foetus of $3\frac{1}{2}$ months, it was considered that valuable information on this subject might be obtained if the position of these groups was found in a foetus in which the internal genital organs were sufficiently small to permit of a complete series of sections being made.

A brief description of the anatomy of the specimen and its histological preparation is necessary before the results of the investigation of the peripheral sympathetic innervation of the uterus can be described.

The specimen was obtained from a patient who died somewhat suddenly from Hyperemesis Gravidarum. The autopsy was carried out less than 12 hours after death. The contents of the pelvis were removed intact. The uterus was then opened, and the foetus extracted. The foetus looked quite fresh, no signs of maceration being evident. From vertex to breech it measured 15 cms. The pelvic bones and lower part of the vertebral column were dissected out carefully, and without damage/

damage to the contents of the foetal pelvis. The peritoneal cavity was then opened from in front, and the foetus divided across a short distance proximal to the internal genital organs. Unnecessary portions of the anterior abdominal wall and of the muscles of the back were then removed, leaving as complete a block as possible of the organs within the lower abdomen and pelvis. This block was fixed in Kaiserling's Formalin solution, and a complete series of 2872 paraffin sections, each 10 microns thick, was prepared. These are numbered from the cranial extremity backwards. While the unsectioned block was in xylol, the vessels and other structures showed up so beautifully that a freehand drawing was made of the upper part of the specimen at this stage (Fig.XII). The block includes the rectum (r) posteriorly, the bladder (b) anteriorly, (portions only of the ureter (ur) being distinct on either side) and between these the genital organs. The ovaries (o) are shaped like bay-leaves, lying with their long axes horizontal. They lie proximal to and immediately above the Fallopian tubes (t). They extend from just within the upturned lateral end of the tube to a short distance medial to the opening of the tube into that portion of the uterus which will form the future body (ut). The anterior surface, as indicated in the drawing, is not smooth, but shows a horizontal groove, from which side branches run as shallow sulci towards the proximal and distal borders.

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The tube on either side passes out from the uterus to terminate in a curve around the lateral extremity of the ovary. In its course it is thrown into small rounded curves encountered in all planes. Relative to its length, the duct is narrower than is the adult Fallopian tube. Other details will be described later.

The drawing shows that the utero-vaginal tube consists of a long cylindrical portion a little narrower than the rectum surmounted by a short broader part which widens out proximally, and which laterally is continued into the tubes. On the cranial extremity of the upper portion a shallow medial sulcus is seen, but no evidence of the presence of a sulcus is found on the anterior surface. There is no indication on the external surface whether the line of demarcation between the distal narrow and the proximal wide portion corresponds to the dividing line between the future body and the cervix, or between the cervix and the vagina.

The blood vessels (v) show up particularly well. On the right hand side, the loose tissue in which they lie had been slightly damaged during the manipulations of the block, and as a result the proximal portions of the vessels were displaced outwards. For this reason, their course is not shown in the drawing. With the exception of a few reserved for special staining methods, the sections were stained with haematoxylin/

haematoxylin and eosin. Microscopically the preservation is good.

A flat reconstruction of the genital tract, Fig.XIII, shows its outline, the lumen being indicated by a dotted line. Remnants of Gartner's ducts, in those parts of their course near to the utero-vaginal canal and to the tubal portion of the uterus, are seen. The tubes are long and narrow, and show the multiple curves already mentioned, but naturally only those apparent in one plane. The free end of the tube has a fimbriated extremity. Its opening faces posteriorly. From the margins of the opening, strands of connective tissue are continued laterally in the edge of the mesosalpinx and also towards the ovary. At the other end, the tubes enlarge to form the tubal portion of the body of the uterus. In the reconstruction, the sulcus on the cranial extremity of the uterus at this stage of development is .4 mm. deep.

There is no median septum in the cavity. The formation of a single roughly symmetrical uterine cavity has kept pace with the union of the tubes to form the tubal portion of the body of the uterus. The unpaired portion of the generative tract is at this stage divisible into three portions:- (1) The most proximal part is somewhat triangular in form, its base forming the future fundus of the uterus: (2) A cylindrical portion with thicker walls and a narrower cavity: (3) A long portion narrower in its proximal than in its distal half and possessing/

possessing a relatively thin wall. The opening of this portion into the urogenital sinus is still closed by a solid mass of tissue. No sharp line of demarcation is present between these three portions. In length their cavities measure approximately 1.4 mms., 2.8 mms., and 5.6 mms. respectively. Diagrams illustrating the contour of a section from each of these three portions are seen in Fig.XIV. The region of the transition between the triangular proximal portion and the remainder is marked externally by the entrance of the ducts of Gartner (d) into the uterine substance. This is therefore probably the dividing line between that portion of the uterine mucous membrane developed from the uterine portion of the tubes and that developed from the utero-vaginal canal. These three portions are taken to correspond with the body of the uterus (ut), cervix (c), and vagina (v), respectively, and later, histological evidence in support of this is given.

The Fallopian Tubes. From the reconstruction, the tubes differ somewhat in measurement. That on the right is 1.12 cms. in length and varies in breadth from 0.02 to 0.8 cm.: the shelf-like formation at its free end makes up 0.14 cms. of its length, the corresponding measurements on the left are 0.92 cms., 0.02 to 0.04 cms., and 0.14 cms. Both tubes pass outwards until opposite the lateral extremity of the ovary. Then they curve upwards and finally terminate by a distinct inclination backwards, thus ending behind the ovary. Each tube possesses

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a canal patent throughout its entire length. The lining epithelium consists of cells whose protoplasm stains deeply. The nuclei are oval, intensely stained and large relative to the size of the cells. In places the epithelium is in the form of a single layer which is definitely columnar in parts. In places no epithelium is recognisable because the walls of the tube are almost in apposition; but a potential lumen is always apparent.

The lumen in its simplest form in cross section has the appearance of a four-rayed star. In this specimen, the two ventral and the two dorsal folds producing this formation are not, as described by Felix (68) in Keibel and Mall in a 50 mm. head-foot length embryo, due almost entirely to difference in height of epithelium, but at this stage are formed of embryonic connective tissue. Towards the outer end of the tube, besides these primary folds, there are secondary ones varying in size and shape.

Regarding the remainder of the wall of the tube, the two coats are distinct which Felix (68) describes in a foetus of 80 mm. trunk length. In my specimen, however, they are approximately equal in thickness. Muscle fibres in the adult sense cannot be recognised. Both coats are well vascularised. The inner has irregularly arranged cells with faintly stained protoplasm and round deeply stained nuclei. The spindle cells of the outer coat

form/

form circular layers. The two coats become ill-defined as they are traced towards the outer end of the tube. The inner coat I regard as the forerunner of the stroma of the mucosa and the outer band as destined to form the muscular layer. This is in agreement with Felix (68) and in the case of the outer band with Bryce (69) who however makes no statement as to the fate of the inner coat.

The tissue of the entire tube is not sharply demarcated from that of the broad ligament. In the boundary zone between run the main vessels of supply to the tube. Near this, the layers, recognisable as serous and subserous by Felix, (68) cannot be made out.

Caudal to the mesovarium the common urogenital mesentery passes forwards and distally to fuse with the connective tissue surrounding the inner end of the tube. Its point of attachment is about 2 mm. lateral to the median sulcus on the cranial aspect of the body of the uterus. The future body will therefore come to include the inner 1 mm. of the present Fallopian tube.

The Body of the Uterus. Regarding that part of the uterus proximal to the level at which the ducts of Gartner enter, we find that the anterior and posterior walls are relatively thick (Fig. XIV A). The walls are formed by a continuation of the two coats already described in/

in the wall of the tube. At this level they become widely separated by a third zone which makes up a considerable thickness of the wall. In this, densely packed clusters of cells are found. The nuclei of the cells of this zone are directed for the most part at right angles to the cavity of the uterus. Into this zone strands of cells turn inwards from the outer circular zone. The presence of these strands suggests that this middle zone represents part of the muscular coat of the fully formed uterus. No sharp demarcation exists between these three portions of the uterine wall. No fully formed smooth muscle bundles are present, but the nearest approach to this is found in the circular zone. Nagel (70 & 71) found smooth muscle arranged in bundles in embryos of 15-22 cms. length. This muscle appeared first under the peritoneal coat.

The cavity enclosed by these walls forms in transverse section a narrow wavy slit as the anterior and posterior uterine walls are for the most part in apposition. The epithelial lining is similar to that in the tube, although again it is absent in places.

The Cervix. This part besides being marked off by the relative uniformity of the width of its cavity, and by the width of its lateral walls (Fig. XIV B) differs from the body in some details. This portion, instead of forming an oval in transverse section is almost circular. The arrangement of the cells of the middle layer of the wall is more irregular than in the body. The increase in depth of the wall of this part is due to an increase in the outer two layers of the wall, i.e., in those layers which will go to form the muscular coat of the cervix.

The epithelium lining the cervix is similar in appearance to that present in the tube and body of the uterus and here also at certain levels is absent. In the middle line into the upper part of the cervical canal there is a longitudinal bulging of the anterior wall. Opposite this prominence there is a longitudinal groove in the posterior wall. This prominence represents possibly the first commencement of the arbor vitae. No evidence is found in this specimen of the secondary folds of mucous membrane, which are described by Felix (68) as arising from the base of depressions in the wall of the cervix in embryos of about 150 mm. The lower end of the cavity of the cervix forms a narrow transverse slit.

The Vagina. Distal to this portion having a narrow slit-like lumen, there is a sudden widening of the genital canal, and a thinning of the walls (Fig. XIV C). This foetus then resembles those described by both Van Eckeren[72] and Mihalkovicz.[73] These observers considered that this dilatation was the first sign of division into vagina and uterus. Van Eckeren described it as occurring in the second half of the fourth month. Mihalkovicz found a slight dilatation below the position of the external os, even in an embryo 14 cms. long. On the other hand Nagel[70] described the first beginning of formation of the portio as an ingrowth of the cubical epithelium into the hind wall. He found this in an embryo of 12 cms. in length, but in one of 14-15 cms. trunk length it did not occur. This is an example of the variation in time at which the portio develops. Other observers bring evidence in support of this variation. Dohrn[74] described the anterior lip in embryos of 15-16 weeks as a half-moon-shaped prominence on the anterior wall of the genital tract. Tourneux and Legay[75] described embryos of 12.5 and 16 cms. trunk length in which the portio is present, whereas in one of 20 cms. trunk length he found only the anterior lip. Geibel[76] found the formation of the posterior fornix occurring only in the 6th month, no anterior fornix even then being present.

Just/

Just as in the more proximal portions of the genital tract, in this specimen the cavity is lined by epithelium, but at various levels it is absent. The epithelium is stratified and non-vesicular. The nuclei of the cells are oval and small relative to the size of the cell and are rich in chromatin. It may now be noted that the character of the epithelium has been of no value in locating the exact limits of the different regions of the tract.

The structure of the remainder of the wall of the vagina differs from that of the uterus. At the junction of the cervix and vagina, the circular layer described in the cervix becomes very thin. Traced distally it soon disappears, as a distinct layer. Otherwise the wall is formed of cells arranged irregularly, although the majority of them run longitudinally, especially in its proximal portion. About 2 mm. from the distal end of the vagina, the urethra becomes intimately associated with the anterior wall, so that the one mass of tissue appears to embrace both structures. The vagina tapers down to end in a short solid portion (Fig.XIII). Gland-like projections of the epithelium of the urogenital sinus pass into this. This distal solid portion of the vagina, for the length of about 1 mm., is enveloped in a band of tissue, like that of the wall

of/

of the urethra. The cells of this tissue stain more deeply with eosin than do those of the wall of the vagina.

That portion of the wall intervening between the distal end of the vagina and the cavity of the urethra is made up of interwoven bundles of cells. In the distal 2 mm.s of this are embedded branching tubules communicating with the urethral canal and lined by epithelium similar to its epithelium. These tubules I regard as representing the prostate gland in the male, which agrees with the finding of Evatt (77) from the examination of a 3½ months old female foetus, and of Keibel (78 & 79) who found the openings of these glands similarly situated. On the other hand, Evatt quotes Gustav Pallin (138) as having found their ducts opening neither into the urethra nor into the vagina, but exactly at the boundary between the two. Around these tubules, in my specimen, spindle-shaped cells are arranged concentrically. In the antero-lateral wall of the urethra only one tubule is seen and it does not penetrate far into the wall of the urethra. The wall of the urethra is thickly beset with minute venous spaces, especially on its antero-lateral aspect.

A. The Cervical Ganglion.

A graph reconstruction (Fig. XV) has been made from this specimen to show the branches of the hypogastric nerve to the uterus, and the position of the groups of nerve cells on these branches. The series of sections extended to the inferior mesenteric ganglia, from which bundles of nerve fibres pass to the intestine along with the inferior mesenteric artery. A median plexus of nerve fibres runs distally anterior to the aorta. The last named in Fig.XV divides about 0.2 mm. distal to the fundus of the uterus, to form the hypogastric nerves (h.n.), along the course of which ganglionic nerve cells are scattered. They are most numerous opposite the cervix (c) in those parts from which the branches supplying the uterus and tubes arise. The hypogastric nerves lie about 0.2 mm. lateral to the wall of the uterus.

On the course of the most proximal of the branches of the hypogastric nerve is a mass of nerve cells (g). This branch passes upwards and anteriorly, giving off a transverse branch to the cervix; continuing its course it divides into two branches which run to the cervix at the level of the future internal os. From these transverse branches, bundles of nerve fibres run upwards, to supply the upper part of the body of the uterus and

the tubes. From the more lateral of these divisions, a small branch (o) is given off, which passes into the hilum of the ovary. The original two branches, running to the uterus at the level of the internal os, communicate with the more distal branches of the main hypogastric nerve by lateral communicating unions in the broad ligament, which lie within 0.1 mm. from the wall of the cervix. The more lateral of these two lies behind the other.

Coming back now to the first branch of the hypogastric nerve mentioned above, about 0.5 mm. distal to it a second ganglionated branch runs transversely towards the cervix, and, as described, communicates with the branches already distributed to the uterus. This particular nerve shows two branches, one of which terminates at the middle of the cervix, and the other at the internal os. Another main branch is given off the hypogastric about 0.6 mm. distal to and communicating with this second branch. This branch comes off below the level of the peritoneal reflexion posteriorly. It supplies the lower part of the cervix, and sends a large branch laterally anterior to the ureter. This latter subdivision has nerve cells upon its course and distributes branches to the bladder. Further distally two other branches of the hypogastric, supplying the lower end of the cervix, can be traced to the wall of the cervix.

Excluding/

Excluding the first branch of the hypogastric the communicating branches of which have been described, the remaining branches communicate with one another in an irregular manner.

It was found impossible to trace out the more distal branches supplying the vagina (v), as they are in such intimate association with the branches both to the rectum and to the urethra and bladder. The connections between the hypogastric plexus and the spinal nerves were necessarily destroyed during the removal of the vertebral column. In this specimen therefore the nerve cells are not confined to form a single cervical ganglion, but are scattered along the divisions of the hypogastric plexus in the region of the cervix.

The sympathetic nerve fibres, supplying the internal genital organs, thus pass down the hypogastric nerves to the level of the cervix, and then pass to the tubes, uterus, cervix and upper portion of the vagina, by several branches which communicate with one another. These branches are intimately associated with branches of of the uterine artery. Nerve cells are scattered along the hypogastric nerves and occur on each of their main branches.

B. Intramuscular Nerve Cells.

No cells similar in size and shape and staining reaction to the nerve cells on the hypogastric nerves outside the uterus were found within the wall of the vagina, cervix, body or tubes. While the majority of the sections were stained with haematoxylin and eosin, a series at intervals was stained by a modification of the methyl green-pyronin method used by Hyrntschak.(66) As these stains showed up only the larger bundles of nerve fibres within the uterine muscles, portions of human uterine muscle from specimens removed at operation were stained by Ranson's modification of Cajal's method and by Sand's method. Using Ranson's method single non-medullated nerve fibres were traced within the muscle wall but no nerve cells were found. By Sand's method only relatively large nerve bundles were demonstrated successfully.

IV. PHYSIOLOGY.

The problem is to determine the part played in the autonomic control by:-

(A) The cervical ganglion;

(B) The intramuscular mechanism.

(A). THE CERVICAL GANGLION.

Two methods were employed - one physiological and the other pharmacological.

(1) PHYSIOLOGICAL METHOD.

In the first place an attempt was made to determine the difference if any in the action of the excised uterus with and without the ganglion. The experiments were carried out under the assumption that, with the treatment which the preparations received, the nerve cells would continue to function after removal from the body.

METHOD.

A series of experiments were carried out on the isolated uterus of the guineapig and of the rat using a modification of the apparatus of Magnus[52] and of Dale and Laidlaw.[80]. (Fig. XVI.).

One glass tube, on to the closed lower end of which three small hooks had been fused and having a perforation above the hooks, was used as an inlet for oxygen and to anchor the muscle strips. The formula of the Tyrode was:-

NaCl 0.8%; KCl 0.02%; $CaCl_2$ 0.02%; (crystals) $NaHCO_3$/

$NaHCO_3$ 0.1%; $MgCl_2$ 0.01% $Na\ H_2\ PO_4$ 0.005%; glucose 0.1%, the $NaHCO_3$ being dissolved before the addition of the $CaCl_2$. In each case the p_H was lowered to 7.4 as at this the uterus of both the rat and the guineapig contracted well. The Tyrode was changed by syphon action without the tissues being exposed. It was introduced from a height through a funnel, through as short a length of rubber tubing as possible, then through a glass tube the cavity of which was continuous with that of the lower end of the bath. A tube passed from the upper part of the cavity of the bath and acted as an overflow exit. The capacity of the bath was 30 ccs. The bath was surrounded by a water bath, the temperature being regulated by heating a projecting limb attached to it. The rubber tubing and funnel were kept when not in use in a large water bath at 37.5°C. The apparatus was only sufficiently accurate to maintain the temperature of the bath between 36.5° and 37.5°C. To ensure greater constancy a more accurate apparatus would be needed such as described by Roth,[83] Eckler,[81] Pittinger,[84] Burn and Dale,[85] or Swanson.[82]

It was found necessary to keep the rate of inflow of oxygen into the bath uniform since if the rate suddenly increased both the tone and the amplitude of the contractions decreased. Lovatt and Underhill[86] found that the tone of plain muscle varied with the rate of introduction even of an indifferent gas.

When/

When the Tyrode solution remained in contact with the uterine strips and exposed to the air and to the stream of Oxygen, its hydrogen-ion concentration was found to change. In two experiments the p_H had increased from 7.5 to 7.8 during intervals of 100 and 110 minutes respectively. The contractions decreased in amplitude the longer the strips remained in the same Tyrode. No attempt was made to determine whether this was in part due to the development of some derivative such as Le Heux[87] and Arai[88] and Magnus[89] described in the intestine, and Engelhard[90] - according to Magnus, and Bachman[91] in the uterus, but, to eliminate error arising from this change, the solutions in the bath were changed frequently.

Material used.

The experiments were made on the isolated uterus of the rat and guineapig. The rats weighed 104-230 grms. and the guineapigs 370-600 grms. The uterus of the mouse was too small for this work. For the experiments in which the ganglionated and non-ganglionated portions were being compared, the uterus of the rat was preferable for two reasons, viz., (1) the absence of the large spontaneous variations of tone which are a feature of the isolated guineapig's uterus contracting in Tyrode P_H = 7.4; (2) the proximity of the cervical ganglion to the uterine wall.

As in each experiment the strips being compared were taken from the same animal it was considered unnecessary to identify the stage in the oestrus cycle which the work of Blair (92) has shown to modify the character of the contractions.

Preparation of the strips.

The animal was killed by a blow on the head and by cutting its throat. In some cases it was given a small initial dose of ether. To facilitate the removal of the broad ligament intact, the anterior wall of the pelvis was removed. The ovaries, uterus and vagina were excised without the muscular part being touched with instruments and were placed at once in Tyrode kept at about 37°C. The strips were treated identically, the risk of injury being reduced by using a very fine needle and silk. The ovaries were detached from the horns before they were placed in position in the bath. The portions of uterus to be compared

differed/

differed in that one was cut away from and one remained attached to the cervix carrying with it the broad ligament including the cervical ganglion. In both the non-pregnant guineapig and rat the preparations were tubular including the entire circumference of the uterus. In the pregnant rat and guineapig when the horns were much distended only a narrow strip was used. They are named for convenience the "non-ganglionated" and "ganglionated" portions respectively. A comparison was made between corresponding parts of opposite horns, uterine and ovarian ends of the same side, and of opposite sides, and between the ovarian end and a portion including the uterine end of the horn and the cervix. The measurement of the preparations was made after they had been overnight in cold Tyrode without oxygen.

RESULTS.

a. Behaviour of either horn of the uterus (1) one with, (2) one without the ganglion.

The contractions in certain rats gave tracings of pendulum-like regularity. (Figs. XVII and XVIII). In others smaller contractions were superadded to the simple waves. (Fig. XIX). The occurrence of these small superadded contractions differed irregularly from one animal to another. Their number might alter and they might show themselves anywhere on the curve. Neither their number nor their position was determined by the presence or absence of the attachment of the cervical ganglion.

Especially/

Especially at the beginning of the experiments variations occurred in the state of tonus upon which the contractions were superadded. The two portions differed in most experiments in irregularity but although in 75% it was greater in the ganglionated part, the number of exceptions prevented this from being attributed to the influence of the cervical ganglion. Some, but not all, of the experiments showed differences between the two portions in the rapidity with which the relaxation followed the contraction and the rate at which the contraction passed off, but there was no difference between the non-ganglionated or ganglionated part. The rate of contraction was greater in the non-ganglionated part in 13%, in the ganglionated in 56% and was equal in both in 31%.

A comparison between the rates of contraction of preparations taken from opposite ends of a horn - both portions being unattached to the ganglion - showed that in 3 out of 4 experiments the rate of contraction of the part from the ovarian end was greater than that from the vaginal end. (Figs. XVII, XVIII, XIX.). This greater rate of the part from the ovarian end was not determined by its length relative to that from the vaginal end, as its rate was more rapid both when it was the longer Figs.XVII and XVIII and when the shorter Fig. XIX. In the remaining experiment, on account of there being smaller contractions superadded to the main contractions, the rate of the portion from the ovarian end

was/

was too irregular for a comparison to be made. These results show that there was some intrinsic difference between a strip from the ovarian and one from the vaginal end of the horn. This agrees with Kehrer (93) who showed that in the cat, dog, and rabbit each part of the uterus shows a different type of contraction. Ogata S. (46) found that the ovarian end contracted more rapidly than the remainder of the isolated horn of the non-pregnant rabbit.

One of the factors therefore determining the variations in the relative rate of the two portions is their position in the horn, and they rarely correspond exactly because during their preparation the horns vary continually in their state of contraction.

b. Behaviour of a Horn of the Uterus (1) before (2) after removal of the ganglion.

A comparison was made between the tracings before and after removal of the ganglion in the following experiments. In each the trauma to the two portions was equalised by a small piece being cut off beyond the end of the non-ganglionated preparation. Any change in the base line of the tracing before and after the operation depended not only on a change in the tone of the horns and on the depth to which they were sunk in the bath but also on the approximation of the levers to the drum. Although therefore a very slight modification of the tone if equally marked in the two might escape being registered, a difference between the two in any change of tone produced, would be demonstrated.

Experiments:

(1) Both portions were taken from the ovarian end of the horn. The longer ganglionated horn contracted the more slowly. After the operation there was no difference between the two portions in the degree of any slight change of tone produced. A decrease in amplitude occurred but this was greater in the part from which the ganglion had not been removed. A slight increase in rate occurred in both horns and this was slightly more marked in the portion from which the ganglion had been removed. No change in the form of the tracing occurred on removal of the ganglion.

(2)/

(2) Both portions were taken from the ovarian end of the horn and were equal in length. Their contraction rates were almost equal.

No change of tone followed removal of the ganglion. A slight decrease in amplitude occurred only in the horn from which the ganglion had been removed. An increase in rate occurred in both horns after the operation but the change was equally marked in the two portions. The form of the tracing was not modified by removal of the ganglion, although slight temporary arhythmia occurred especially in the deganglionated preparation. (Fig. XX).

(3) Both portions were taken in this experiment from the ovarian end of the horn. Their length and their rate of contraction were practically equal. There was no difference between the two horns in the degree of any slight change of tone produced by the removal of the ganglion. An equal increase in amplitude occurred in the two. The increase in rate was slightly less in the horn from which the ganglion had been removed. (Fig.XXI).

The same operation was also performed in the following four experiments, in which, however, the horns had been treated already by Physostigmin* 1:6200 or by Pilocarpin 1:5000 or 1:2500. Although these drugs are not known to poison the ganglion in these strengths their previous use lessens the value of the experiments.

(1) The portions (taken from near the ovarian end) had been treated with Physostigmin 1:6200.

No change in the form of tracing occurred on removal of the ganglion. Before removal the rate of the shorter ganglionated horns was the greater but no decrease in rate followed the removal of the ganglion.

(2) The comparison was made while the portions (taken from near the vaginal end) were contracting in Physostigmin 1:6200.

No change in rate nor in the form of the tracing was observable on removal of the ganglion.

(3) Between the tracing before and that after the removal four hours had passed during which the horns had been treated at intervals with Pilocarpin Nitrate 1:2500. During this time a decrease in rate which was if anything greater in the non-ganglionated portion had occurred.

Before/

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* In this paper the mode of spelling the names of the alkaloids without a terminal 'e' has been adopted.

Before removal of the ganglion the rate of the longer ganglionated horn was the more rapid and this greater rate persisted after its removal. No change was observable in the type of contraction on the removal of the ganglion.

(4) In this experiment the tracings being compared were recorded at an interval of two hours during which the horns had been treated with Pilocarpin Nitrate 1:5000 and 1:2500.

Initially the contraction rate was greater in the shorter ganglionated portion. A decrease in rate had occurred in both upon removal of the ganglion although this decrease was slightly greater in the deganglionated portion. Associated with the removal of the ganglion no other change in the tracing had occurred. It is worthy of note that this experiment differs from the other three in that a portion of the vaginal end of the horn was removed along with the cervix and ganglion. It may be that this explains the decrease in rate.

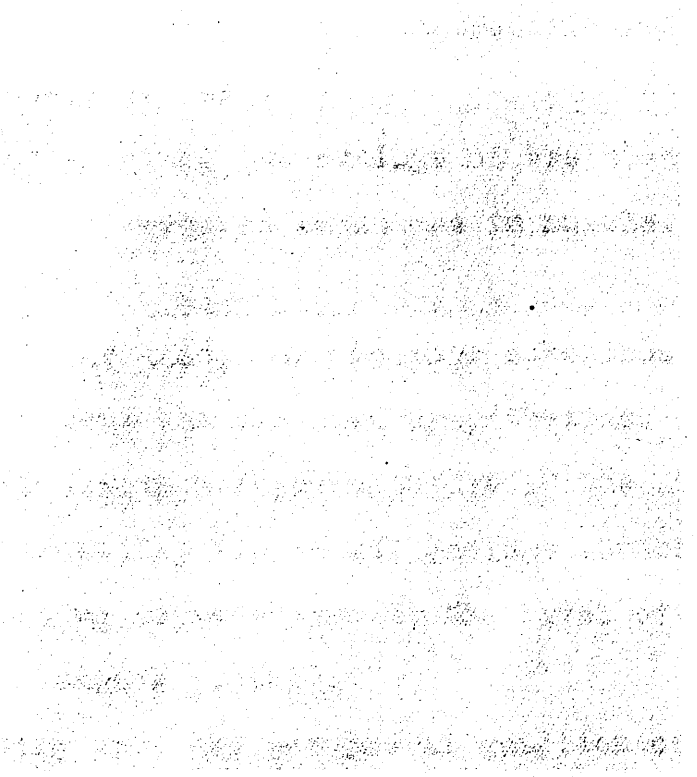
Conclusions.

(a) This method of investigation affords no evidence of any direct action of the cervical ganglion on the movements or tone of the excised uterus. This finding agrees with that of Kehrer (93) who stated that the form of contraction typical of each specific part of the genital tract in the rabbit, cat and dog, was unaltered by the removal of part of the surrounding pelvic tissues or their complete removal up to the muscle wall.

(b)/

(b) The point of origin of the impulse initiating and controlling the movements of the uterus therefore appears to lie within the uterine substance itself.

(c) The rate of the contractions occurring at the ovarian end is quicker than at the vaginal end of the horn.



(2) PHARMACOLOGICAL METHOD.

It seemed that a study of the action of drugs - known to act upon the peripheral nervous mechanism of viscera - upon the uterus with and without the cervical ganglion might throw further light upon its possible action.

For this purpose the following drugs were selected -

(1) Barium as acting directly on the contractile substance of muscle. (Cushny p. 569).(94)

(2) Adrenalin as stimulating the endings of the true sympathetic neurones or their receptor substance in muscle. (Cushny p. 372.)

(3) Pilocarpin as stimulating the receptor substance of the true and the para-sympathetics. (Cushny p.342)

(4) Physostigmin or Eserin, a representative of the Muscarin group, as stimulating the neural endings (Cushny p.351).

(5) Atropin as blocking nerve action at the level of the receptor substance. (Cushny p. 323).

(6) Nicotin as acting upon the peripheral ganglion cells, first to stimulate and then to paralyse. (Cushny p.314).

(7) Ergotamin and Ergotoxin stimulating and then paralysing the augmentor receptor substance. (Cushny p.377).

To make such a clear cut classification is ofcourse unwarranted/

unwarranted since the characteristic action of each substance depends upon the concentration, i.e. the dose, and upon the condition of the structures acted upon. Not only may the stimulating action of a moderate dose be converted into a paralysing action by larger doses, but the mere continuance of the presence of the drug may alter the reaction of the tissues to it. Further while the primary action may be upon one of the tissues present, e.g. upon say the receptor substance, greater concentration or prolonged action may result in a spread of the effect to other parts.

In the following description of the action of these drugs the tone and contractions although not necessarily independent are dealt with separately. As regards the contractions their rate and amplitude were measured. The relation of tone and amplitude is somewhat complicated. There may be a concomitant increase of both. On the other hand a marked increase of the tone may decrease the amplitude of contraction.

In the experiments the preparation of the drugs used were:-

(1) Barium Chloride.
(2) Solution Adrenalin chloride P.D. & Co., 1:1000.
(3) Pilocarpin nitrate B.P. 1914. The British Drug Houses London.
(4) Eserina. The British Drug Houses London.
(5) Atropin sulphate.
(6) Pure Nicotin and Nicotin tartrate. The British Drug Houses London.
(7) Ergotoxin phosphate kindly given by Dr Dale.
Ergotamin tartrate, Femergin, "Sandoz."

(a) The Action of each of these on the isolated Uterus of the Rat and of the Guineapig.

(1) Barium.

Previous workers report as follows:-
In the cat Kehrer (93) obtained strong contraction with Barium. Fardon (95) gives a tracing showing the increase in tone and the onset of contraction produced in the guineapig's uterus by administration of 8 mgs. of Barium Chloride. Itagaki (96) found that a concentration of 1:100,000 produced an increase in tone of the isolated uterus of the rat while stronger it produced pronounced contraction. Ogata S. (46) in the rabbit cut the broad ligament on one side so as to sever the nerves to the uterus and after 21-82 days excised the uterus and compared the action of Barium on the horn of the operated and non-operated sides. He found that in both there was an increase in tone and in the frequency of the contractions but the response was greater on the operated side. This he considered showed that some alteration in the tone of the muscle had been produced by denervation. In the investigation which is here described Barium caused an increase in tone in all the experiments on the rat's uterus. This was associated with an increase in rate of the contractions. In weak solution 1:75,000-1:10,000 there was an/

an increase, see Fig. XXII in their amplitude whereas stronger solutions produced a decrease in amplitude or their disappearance. (Fig. XL.).

On the uterus of the guineapig a marked augmentor effect was also produced by Barium Chloride in solutions varying from 1:2,500-1:1,670. (Fig. XXIII).

This confirms the work of Itagaki[96] on the isolated uterus of the rat and of Fardon[95] on the guinea-pig's uterus in situ.

(11). Adrenalin.

The effect of Adrenalin on the uterus varies in different species of animals reproducing the effects of stimulation of the sympathetic nerve supply (Langley,[97] Elliott[59] and many others).

In the cat the effect on the uterus isolated or in situ varies according to whether it is pregnant or non-pregnant. Kehrer,[93] Hilz,[98] Barger and Dale,[99] Dale,[100] Cushny,[101] Quagliariello,[102] Bachman and Lundberg[103] and Dale and Laidlaw[104] obtained pure inhibition of the non-pregnant uterus. Both Kuroda[105] and (according to Trendelenberg)[106] Okamato obtained a weak augmentor effect before or after the inhibition. On the uterus of the pregnant cat Kehrer,[93] Kuroda,[105] Okamoto,[107] Cushny,[101] Quagliariello,[102] Bachman - Lundberg,[103] all obtained a pure augmentory effect.

Adrenalin produces contraction of the non-pregnant uterus of the cow. (Meyer).[108] In the dog the effect of Adrenalin varies with the physiological condition of the uterus. In the non-pregnant both an inhibitory and an augmentory reaction have been described. Kehrer[93] obtained inhibition, Kuroda[105] contraction, and Hilz[98] obtained inhibition of the uterus of a dog in heat though a larger dose produced an increased amplitude of the contractions. On the other hand the pregnant uterus is stimulated to contract by Adrenalin (Neu).[109]

On/

On the uterus of a virgin ferret Dale[110] and also Bachman and Lundberg[103] found that Adrenalin produces an augmentory effect.

Most investigators have found that Adrenalin produces inhibition of the uterus of the guineapig whether pregnant or non-pregnant. (Niculescu,[111] Cow,[112] Adler,[113] Okamoto,[107] Gunn and Gunn,[114] Sugimoto,[115] Hilz,[98] Bachman and Lundberg).[103] Occasionally an augmentor effect has followed its use in the pregnant animal (Kehrer[93] and Quagliariello)[102] Sugimoto[115] observed in one guineapig that after intravenous injection of Adrenalin marked anaemia occurred and the uterus contracted tonically.

In both the pregnant and non-pregnant human uterus Adrenalin has an augmentor effect. (Kurdinowski,[7] Kehrer,[93] Neu,[109] Turolt[116] and according to Trendelenberg this was also found by Rubsamen.[117]

Dale[100] obtained with Adrenalin a weak motor effect on the uterus of a virgin monkey.

Whether pregnant or non-pregnant the uterus of the mouse is inhibited by Adrenalin (Adler[113] and Bachman and Lundberg).[103]

In the rabbit whether pregnant or non-pregnant Adrenalin stimulates the uterus to contract. (Kehrer[93] Langley,[97] Kurdinowsky,[7] Okamoto,[107] Gaddum).[118]

Both/

Both Gunn and Gunn (114) and Okamoto (107) obtained an inhibitory response in the pregnant and non-pregnant rat with Adrenalin.

The effect of Adrenalin in concentrations varying from 1:50,000,000 to 1:85,000 was tested in 18 of my experiments and it was found that both in the pregnant and non-pregnant uterus of the rat there occurred a decrease of the rate and amplitude of the contractions, in most cases the contractions ceasing temporarily (Fig. XXIV).

Fig.XXV shows a tracing recording the effect of a weak solution 1:40,000,000 upon the ganglionated horn of a non-pregnant rat. In some experiments both on the non-pregnant (Fig. XXIV) and pregnant rat (Fig. XLVII.) decrease of the tone was also obtained.

The response to Adrenalin in concentrations varying from 1:1,000,000 to 1:16,000 was also found to be an inhibitory one in the pregnant (Fig.LIII) and the non-pregnant (Fig.LIV) uterus of the guineapig. In ten experiments the uterus was non-pregnant and in two pregnant.

The experiments reported upon in this paper confirm the work of Gunn and Gunn (114) and Okamoto (107) on the rat and of those investigators who describe an inhibitory response in the non-pregnant and in the pregnant guineapig.

In these animals the inhibitory mechanism of the sympathetic appears to be the more potent.

(LII). Pilocarpin.

Dale and Laidlaw[14] consider that the stimulating action of Pilocarpin on the uterus of the intact animal is the algebraic sum of three factors, viz. stimulation of sympathetic ganglia, acceleration of the setting free of Adrenalin and a direct motor effect on the uterine muscle. Cushny,[101] working on the uterus of the cat in situ, showed that Pilocarpin causes contraction in the pregnant and inhibition in the non-pregnant condition, its action being completely antagonised by Atropin. In the isolated non-pregnant uterus of the cat, Kehrer,[93] Dale and Laidlaw[14] and Okamoto[107] obtained an augmentor effect with Pilocarpin. In situ, although in most cases complete inhibition followed injection of Pilocarpin, Cushny[101] also obtained an increase in rate and strength of the spontaneous contractions, or, when these were absent, a marked and prolonged contraction followed by a series of smaller waves during relaxation, and in some cases a series of secondary contractions superposed on the spontaneous movements. On the uterus of the pregnant cat, Fardon[95] and Cushny[101] found that Pilocarpin produced augmentation. Fardon[95] compared the effect of Pilocarpin on the separated cornua, finding that after treatment with Ergotoxin for half an hour relaxation of the ergotised cornu occurred instead of this augmentation.

On the non-pregnant uterus of the guineapig both when isolated (Okamoto[107] and Dale and Laidlaw,[14] Sugimoto)[115] and when in situ

Dale/

(Dale and Laidlaw)[14] Pilocarpin has an augmentor effect. This motor effect of Pilocarpin in the virgin guineapig the latter found occurred even after the strip had been treated for 10 minutes with Ergotoxin. Treatment of the pregnant isolated guineapig's uterus with Pilocarpin sometimes produced no effect but more frequently produced contraction antagonised by Atropin (Gunn and Gunn.)[114]

Cushny[119] and Okamoto[107] and Ogata S.[46] found that Pilocarpin produced an augmentory effect on the rabbit's uterus, in the isolated uterus of the virgin rabbit causing (Ogata)[46] sometimes only an increase in rate and sometimes an increase in tone.

Upon the uterus of the rat the results of different investigators are very contradictory. Gunn and Gunn[114] report that Pilocarpin had very little effect and that usually it was a slightly motor effect although in 2 rats (one pregnant and one non-pregnant)[107] it was an inhibitory one. Okamoto describes the production of powerful contractions in the rat's uterus but the concentration of Pilocarpin used was not mentioned, in the Abstract available. Itagaki[96] using concentration varying from 1:100,000 to 1:1000 made up with Locke usually obtained an augmentory effect but occasionally an inhibitory one. Neither Gunn and Gunn nor Itagaki specify the dose with which these inhibitory/

inhibitory results were obtained.

The response of the isolated uterus of the rat to Pilocarpin nitrate in concentrations varying from 1:10,000-1:2,000 was studied in six of my experiments. In each experiment two or three portions were compared at once. The effect was found to be inconstant. In four experiments one or other of the horns showed very little response to Pilocarpin - only a slight increase in rate being observable. An increase of the tone and of the amplitude (Fig. XXVI) and rate of the movements was the most frequent sequel to treatment with Pilocarpin. Occasionally a decrease in rate occurred. Preparations taken from the ovarian and uterine end of the same horn differed in response but no variety of response was observed to be characteristic of either end of the horn. In two experiments - both pregnant rats - decrease in tone and in the rate and amplitude of the contractions occurred, but in each case only in one of the strips under comparison. (Fig.XXVII). In one experiment this strip had already given an augmentor response to a weaker solution of Pilocarpin, 1:5,000. Augmentation was produced in the other strip in this experiment by Pilocarpin in the stronger (1:2,500) (Fig.XXVII) as well as in the weaker solution (1:5,000). In the other pregnant rat no response took place in the other horn, although the solution was fairly concentrated (1:2,000) (Fig.XXVIII).

In/

In both the pregnant and the non-pregnant uterus of the guineapig I found that a slight augmentor effect was produced by Pilocarpin (1:5000-1:2000.) Fig. L.

These results confirm the findings of previous workers who found that the action of Pilocarpin on the uterus of the rat and guineapig is generally augmentory but may in some cases be inhibitory. The inhibition produced in the uterus of the two pregnant rats by strengths of 1:2000 and 1:2500 is difficult to explain. It was not due to a more prolonged action as it occurred immediately in each case. In one experiment the uterus had not been treated before with Pilocarpin. In the other an augmentory effect had been got before with Pilocarpin 1:5000 and was again got with 1:2500 later in the experiment. This also is against its being due to greater concentration, as is also the fact that in each experiment it was obtained only in one of the 2 strips.

(IV). Physostigmin. (Eserin).

On the isolated uterus of the cat, bitch, guineapig and rabbit under all conditions Fardon (95) found that Physostigmin augmented the movements and the tone. This augmentation was better maintained than was that produced by Pilocarpin and was elicited by smaller doses. He reported that it occurred after Atropin "and was not apparently influenced by Atropin". It also produced its effects after Nicotin. Kehrer (120) in 1908 obtained a more distinct augmentor effect on the isolated horn of the cat than with the same dose of Pilocarpin.

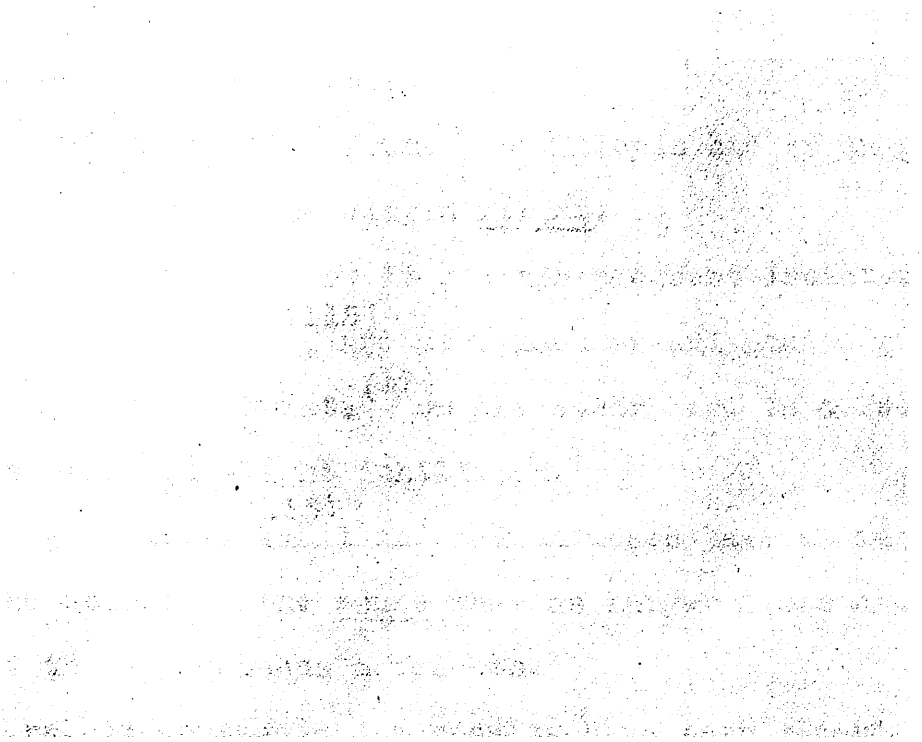
Working on the pregnant andnon-pregnant cat Cushny (119) found that it produced contraction of the uterus and had no apparent effect in causing inhibition but that it was completely antagonised by Atropin (thus contradicting Fardon).

In my investigation the effect of Physostigmin sulphate (1:775-1:3000) was recorded on the uterus in 5 rats - one only being pregnant. After weaker solutions very little response was seen in some strips but the usual effect was an increase in tone and in the rate and amplitude of the movements, Figure XXIX & XXXVIII Strengths of 1:775 and of 1:1550 in the case of certain strips produced a decrease of tone Fig.XXX and of the rate and amplitude of the contractions.

An/

An augmentor effect was produced in both the non-pregnant and pregnant uterus of the guineapig using the strengths (1:4,600 - 1:800). Fig. L11.

An inhibitory effect following Physostigmin has not before been recorded in the literature available to me. These results probably illustrate the fact that while moderate doses stimulate large doses depress and paralyse.



v. Atropin.

Kehrer,[93] on treating the isolated uterus of the cat with Atropin found that with small doses the amplitude of the movements and their regularity increased whereas with larger doses, after the increase, a decrease in amplitude occurred. Bachman and Lundberg,[103] however, obtained no apparent action on the uterus of the cat in situ.

In the dog Kehrer[93] got a similar effect to that obtained in the three cats tested (see above).

Bachman and Lundberg[103] found that Atropin had an augmentor effect on the uterus of the virgin ferret.

Both in the pregnant and in the non-pregnant isolated uterus of the guineapig Sugimoto[115] and also Bachman and Lundberg[103] obtained an increase in tone. Holste[17] on the other hand in a recently pregnant one observed slight inhibition.

According to Adler[113] small and medium doses have an augmentor effect on the uterus of the mouse whereas larger doses cause cessation of the spontaneous movements.

On the rabbit contradictory results have been recorded. Röhrig,[35] Franz,[121] Kurdinowsky,[122] Cushny,[101] and Ogata[46] obtained very little effect. Okamoto,[107] however, found that on the isolated uterus fairly strong doses increase the tone and amplitude of the contractions whereas stronger doses cause paralysis and Franz[121] obtained/

obtained inhibition on the excised uterus. Itagaki (96) describes the effect of Atropin 1:20,000-1:1,000 upon the uterus of the rat. With a concentration of 1:20,000 he obtained an increase and with a strength of 1:10,000 a diminution in the amplitude of the contractions; even with 1:1,000 he failed to get complete inhibition.

That Atropin even in its small doses has an effect on the uterus is shown by its antagonism to Pilocarpin whether the Pilocarpin has produced as in the rabbit and pregnant cat marked contraction or as in the virgin cat in most cases complete inhibition, (Cushny).(119) Fardon (95) showed that this antagonism exists even when acting upon the isolated uterus.

In 11 experiments strips from the horn of the rat - 2 only being pregnant - were submitted by me to treatment with Atropin (1:200-1:2,000). With the relatively weaker solutions an increase in tone associated with a decrease in amplitude and an increase in rate occurred. (Figs.XXXI and XLV.). Stronger solutions produced an inhibitor effect especially if the increase in concentration occurred suddenly. It is to be noted that the strengths used are not the same as those used by Itagaki.

In the guineapig - 3 being non-pregnant and 1 pregnant - slight/

slight augmentation was recorded on treatment with Atropin sulphate 1:1,000. (Fig. XXXII).

The in-hibitory effect obtained is probably an example of the depressor effect of any drug in very strong concentration.

vi. Nicotin.

The effect of Nicotin upon the uterus of the cat whether isolated or in situ varied with its physiological condition. In the non-pregnant cat's uterus, Cushny,[101] Kehrer,[93] Fardon[95] and Okamoto[107] observed that this was followed by an augmentor effect. Dale and Laidlaw[14] however sometimes got no response, sometimes an augmentor effect and with larger doses inhibition, and showed that the effect on the uterus in situ was modified by the outpouring of Adrenalin which followed the injection of Nicotin. Hakan[123] obtained on the isolated cat's uterus an increase in amplitude and rhythm with small doses and with larger doses a transitory increase in tone followed by decrease in rate. Fardon[95] showed that on the isolated uterus of the cat previously ergotised so that only the inhibitor fibres were responsive, Nicotin produced relaxation followed by a gradual recovery of the tone and of the movements. On the pregnant uterus Cushny[101] found that Nicotin produced powerful tonic contraction upon which stimulation of the hypogastric nerves had no effect.

In the human uterus Nicotin produced contraction (Franz),[121] Dale and Laidlaw,[14] and Sugimoto[115] obtained no marked action on the isolated uterus of the guineapig although when the uterus

was in situ (according to Sugimoto) contraction followed treatment with Nicotin. On the isolated uterus Hakan (123) obtained with small doses an increase in amplitude and rhythm and with larger doses a transitory increase in tone followed by slowing of the rhythmical movements.

The effect of Nicotin on the rabbit's uterus differs according to whether it is isolated or in situ. On the isolated uterus following the transitory inhibition Okamoto (107) got increased tone and increased rhythmic movements and Ogata (46) an increase in the rate of the movements. Hakan (123) however found the effect on the isolated guineapig to be an increase in amplitude and rhythm with smaller doses, but with larger doses an increase in tone followed by a decrease in rate. In situ Cushny (101) and Franz (121) obtained an augmentor effect. In the rat Itagaki (96) reported that the effect of Nicotin varied with its concentration. Strengths from 1:10000 to 1:5000 caused an increase of tone; with stronger solutions, e.g. 1:1000 there was at first an arrest of the contractions and then an increase of tone; whereas very strong solutions produced pure inhibition.

The action of pure Nicotin (1:5000 - 1:1000) upon the uterus was studied by me in five non-pregnant rats. It was found to be inconstant - In some strips very little response occurred; Fig. XXXIII, in others an inhibitory and more frequently an augmentor effect/

effect was recorded. Fig. XXXIV and XLVI. In two other rats, Nicotin tartrate was used (1:2500 - 1:1000) and very little effect was seen.

In the uterus of the guineapig (2 non-pregnant and 1 pregnant) only a slight augmentor effect was observed with solutions varying in strength from 1:10,000 - 1:1,250. Fig.XXXV

The action of the Nicotin on the uterus of the rat and guineapig thus seems to be similar to its action upon ganglia - first a stimulation and then a paralysis.

vii. Ergotoxin or Ergotamin.

Contractions of the uterus upon treatment with various ergot preparations have been described. Jacobj[124] observed in the uterus of the pregnant cat rhythmic waves following intravenous injection of Chrysotoxin. He quoted Kobert[125] as having described tetanus uteri following treatment with sphacelinic acid and rhythmic contractions occurring after cornutine.

Kurdinowsky[7] obtained contraction of the isolated uterus of the rabbit perfused with sphacelinic acid.

On the uterus of the cat Dale[100] observed with Chrysotoxin a marked motor reaction. The non-pregnant uterus showed a distinct development of tone and some increase of the amplitude of the rhythmic contractions whereas the pregnant reacted by larger contractions of longer duration.

Ergotoxin was shown by Dale and Laidlaw[14] to have a relatively slight augmentor effect on the isolated non-pregnant uterus of the cat. Dale and Barger[126] showed that this effect was more marked than that produced on the rabbit's uterus in situ. Rothlin[127] has not been able to confirm the presence of a noticeable difference between the action of ergotamin on the rabbit and cat.

Rothlin[128] described a remarkable augmentation accompanied by rhythmic movements following intravenous injection of ergotamin into/

into the cat.

Dale and Spiro[129] have shown that there is no difference between the augmentor effect produced on the isolated uterus of the virgin cat by Ergotamin and that by Ergotoxin.

On the isolated uterus of the guineapig Clark and Broom[130] obtained an augmentor effect. Spiro[131] showed that in the non-pregnant and pregnant uterus although an increase in tone and rhythm occurred on the upper half of the uterine horn, at the same time it produced relaxation of the lower cervical end of the horn.

Rothlin[128] obtained the augmentation upon the uterus in situ. Dale and Spiro[129] showed that ergotoxin caused an augmentor effect on the virgin guineapig's uterus similar to that following treatment with Ergotamin.

Spiro[131] observed augmentation of the human uterus upon treatment with Ergotamin.

In the virgin monkey Dale[100] described a distinct augmentor effect on the non-pregnant uterus.

On the uterus of the rabbit whether isolated (Schegg)[132] or in situ (Rothlin)[128 & 133] and both in the pregnant and non-pregnant state ergotamin causes augmentation. Dale,[126] however, only got a very slight augmentation of the natural rhythm of the uterus in situ upon treatment with Ergotoxin.

On/

On the isolated uterus of the rat Dale[129] obtained a slight but equal augmentor effect both with Ergotamin and with Ergotoxin. The latent period was shown by Spiro[131] to be long but once established the augmentor effect persisted one hour or more (Rothlin)[128] even after washing of the organ (Spiro).[131]

Dale[100] showed that Ergotoxin reversed the action of adrenalin on the cat in vivo. Clark and Broom[130] and Schegg[132] showed that this applied for Ergotamin (Gynergen) on the isolated rabbit's uterus.

In the two experiments that I made upon the rat a slight increase in tone, amplitude, and rate, was produced by Ergotoxin (1:2,500,000). In Fig. XXXVI a strength of 1:10,000,000 is seen to have produced an increase in amplitude. (The Ergotoxin phosphate was very kindly given by Dr Dale.) An augmentor effect also followed the treatment of the uterus with Ergotamin tartrate (1:100,000). (Ampulles Sandoz Chemical Co.). In the pregnant uterus of the guineapig I found that Ergotamin tartrate (1:1,000) produced slight augmentation. (Fig. XXXVII).

These results agree with the previous work done upon the uterus of the rat and the guineapig. Both are relatively irresponsive to these drugs. This may be partly due to the preponderant activity of the inhibitory mechanism in these animals.

(b) The Action of each of these Drugs on the Horn of the Rat with and without the Ganglion.

The results of the action of each drug on the isolated uterus of the rat is described on pages 51 to 71.

(1). Barium caused an increase in the tone and an increase in the rate of the contractions. The presence or absence of the ganglion attached to the horn did not affect, Fig.XXll the degree of the increase in tone or in the rate of the contractions nor did it alter the change in amplitude which increased with weaker and decreased with stronger solutions of Barium Chloride.

(2). Adrenalin always caused inhibition. The intensity of the inhibition produced by Adrenalin was not modified by the presence or absence of the ganglion attached to the horn. Fig.XXlV

(3). Pilocarpin produced very little effect on some strips but an augmentor response was its more frequent sequel. In two pregnant rats, however, inhibition resulted.

The nature of the response to treatment with Pilocarpin and the extent of the change produced did not depend upon the presence or absence of the ganglion. (Fig.XXVll) / In the two pregnant rats in which a decrease of the tone and of the rate and amplitude of the contractions occurred, this inhibition was seen only in the horn attached to the ganglion in one experiment, Fig.XXVll and only in the one unattached to the ganglion in the other. Fig.XXVlll

(4/

(4) Physostigmin caused most frequently an increase in tone and in the rate and amplitude of the movements. Larger doses produced an inhibitory effect. The presence or absence of the ganglion attached to the strip did not affect the character and degree of the effect, Figs. XXIX and XXXVIII.

(5) Atropin except in very strong solutions produced an increase in tone associated with a decrease in amplitude and an increase in the rate of the contractions. The response to Atropin was not modified in its degree or character by the presence of the ganglion. (Figs. XXXI and XXXII).

(6) What response Nicotin produced either inhibitory or augmentory, the intensity and nature of the change did not depend upon the presence or absence of the ganglion. (Figs. XXXIII, XXXIV and XLVI.)

(7) Ergotoxin or Ergotamin.

The slight augmentor effect following either Ergotamin or Ergotoxin occurred irrespective of the presence or absence of the ganglion (Fig.XXXVI).

Conclusions.

No evidence has been obtained of the cervical ganglion having an autonomic action in controlling either the tone of the uterine muscle or the rate or amplitude of its movements, and, by a process of exclusion, we are therefore led to surmise that the control of the uterine movements must be maintained by the intramuscular neurones.

B. THE INTRAMUSCULAR NEURONES.

In studying the possible action of these the pharmacological method is alone available. It is impossible to sever the connection of the cervical ganglion with the uterus during life so as to allow degeneration to occur. Nor is the evidence conclusive that a degeneration of the ganglia would occur. McIlroy[134] on the retina and Pollock[135] on the iris have shown the nutritional independence of peripheral ganglia. Langley[136] however observed degenerative changes to follow section of the nerves supplying any artery of the skin or muscle of the frog and Fletcher[137] found that section of the pudic nerve with excision of the first pelvic ganglion was followed by degeneration of the nerve plexus in the retractor penis of the hedgehog.

Antagonism.

The action of these various substances having been determined upon the uterus of the rat and guineapig, it was thought that further light might be thrown upon the nature of the peripheral neuronic mechanism by a study of their antagonism. This aspect of the subject has been little dealt with by previous investigators.

(1). Barium.

(1) Barium and Adrenalin.

In both the rat and the guineapig Barium Chloride 1:1670 produced an augmentor effect even when the strip had been treated with Adrenalin/

Adrenalin of sufficient strength 1:166,700 to produce marked inhibition. Fig. XXXIX shows the production of an increase in tone by Barium Chloride 1:1250 upon a rat's uterus under the action of Adrenalin 1:166,700.

Adrenalin 1:200,000 and 1:166,700 on the other hand produced its inhibitor effect upon uterine muscle already under the influence of Barium Chloride 1:2500-1:1670. In Fig. XXIII Adrenalin 1:200,000 is seen to cause a decrease in the tone of a guineapig's uterus already treated with Barium Chloride 1:2,500.

Apparently Adrenalin either stimulates the inhibitor nerve mechanism so powerfully as to overcome the direct action of barium or it acts on the contractile substance as well as upon the sympathetic endings. If the former, evidence is afforded of the existence of a peripheral inhibitory nerve mechanism.

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(2). Barium and Atropin.

In the non-pregnant rat Barium Chloride produced a further effect after the strip had been treated with Atropin Sulphate 1:500 which had caused augmentation. This increase in tone, however, fell away steadily and no movements were present. Atropin 1:1000 in another non-pregnant rat produced a fall in the augmented tone following Barium Chloride 1:1000. (Fig.XL) / The transitory increase in tone in the first experiment is probably the effect of Barium superadded to that of Atropin. Barium Sulphate however is formed and this being insoluble in Tyrode it ceases to act upon the uterus. The ensuing fall in tone may point to Atropin Chloride being more completely ionized than the corresponding concentration of Atropin Sulphate and so producing an inhibitory effect similar to that produced by a more concentrated solution of Atropin sulphate.

(3). Barium and Physostigmin.

Barium Chloride produced no further effect upon the horn of a non-pregnant guineapig already treated with Physostigmin 1:9000. This is compatible with Barium and Physostigmin both stimulating the contractile substance, the latter having produced the maximum effect, or even with Physostigmin stimulating the neural endings.

(4). Barium and Nicotin.

Hakan (123) found that a dose of Nicotin which antagonised the augmentor effect of Adrenalin on the isolated uterus of the cat, rabbit or guineapig was without influence on the uterus already treated with Barium/

Barium Chloride.

I found that in a non-pregnant rat in which Nicotin 1:1000 itself called forth no marked effect and Barium Chloride 1:2500 only an augmentation of the movements, each, when superadded to the other, caused the uterus to contract tonically, having manifestly some synergic action. Fig.XL1

(ii). Adrenalin.

(1) Adrenalin and Pilocarpin.

Upon a non-pregnant rat's uterus on which Pilocarpin 1:2000 had already produced an augmentation of the movements Adrenalin 1:100,000 produced a marked inhibitory effect. Fig.XL11

(2). Adrenalin and Physostigmin.

In the non-pregnant rat Adrenalin caused inhibition in a strip already under the augmentor influence of Physostigmin 1:2500. Fig.XL111 In a pregnant rat, after the concentration of Physostigmin had been increased to 1:775 which had a depressing effect, no further inhibition was produced by Adrenalin. On the other hand in the pregnant uterus of the guineapig Physostigmin 1:4600 was followed by an augmentor effect even although the strip was already under the inhibitory influence of Adrenalin 1:100,000, Fig.XL1V

These results correspond to those obtained by combining Barium and Adrenalin. They therefore tend to establish the conclusion that Physostigmin and Barium act on the same part namely the contractile substance itself. This being so Adrenalin either stimulates the inhibitor/

inhibitor nerve mechanism sufficiently to overshadow the direct action of Physostigmin, or Adrenalin too acts on the contractile substance.

(3) Adrenalin and Atropin.

In the rat Adrenalin produced inhibition in a strip already under the influence of Atropin (Fig. XLV); but on a strip treated with Adrenalin, Atropin produced no effect.

In the guineapig too I found that Adrenalin produced inhibition of an atropinised strip.

The action of Adrenalin seems therefore to be a more peripheral one than Atropin and therefore to act on the receptor substance or contractile substance.

(4) Adrenalin and Nicotin.

After treatment with Nicotin causing an augmentory, or an augmentory followed by an inhibitory, effect, the uterus of the rat and of the guineapig gave an inhibitory response to Adrenalin. Fig. XLVI shows this inhibition following Adrenalin 1:400,000.

In one guineapig, Nicotin 1:1,250 which had produced already an augmentory effect, when used after Adrenalin produced a further fall of tone.

Accepting the action of Nicotin as stimulating before paralysing the nerve cells this is what might have been anticipated (123)
This does not confirm the work of Hakan who found that in the isolated uterus of/

of the cat, rabbit, and guineapig, Nicotin in small doses antagonised the augmentor effect of Adrenalin.

(5) Adrenalin and Ergotamin or Ergotoxin.

In the guineapig and rat Adrenalin produced an inhibitor effect on a strip already treated with Ergotamin tartrate.

In Figure XLVII Ergotamin 1:1000 is seen to produce an increase in tone and amplitude of a strip from a pregnant rat already under the action of Adrenalin 1:166,700.

A comparison between the effect of Adrenalin 1:50,000,000 before and after treatment of the strip with Ergotoxin phosphate showed that a decrease in tone was produced after whereas only a decrease in rate and amplitude before. Figure XLVIII

This greater inhibitory action of Adrenalin 1:50,000,000 after than before treatment with Ergotoxin phosphate may point to the existence within the uterine wall of augmentor neurones which have been thrown out of action by Ergotoxin.

(iii) Atropin.

(1) Atropin and Pilocarpin.

In the horn of the rat upon which Pilocarpin had produced no change or a decrease in tone, subsequent treatment with Atropin caused an increase in tone (Fig. XLIX).

In the pregnant guineapig Atropin 1:1,000 produced very little effect on a uterus under the influence of Pilocarpin 1:5,000. The reverse also held. In the non-pregnant where Pilocarpin 1:2,000 had caused an increase in tone Atropin 1:1,000 caused a decrease (Fig. L). Gunn and Gunn (114) found that on the pregnant isolated uterus of the guineapig Pilocarpin sometimes produced no effect but more frequently contraction antagonised by Atropin. The fact that the action of Pilocarpin is antagonised by Atropin indicates that the point of action of Pilocarpin is proximal to or on the receptor substance.

(2) Atropin and Physostigmin.

In the non-pregnant rat after treatment with Physostigmin 1:3,000 producing an augmentor effect, Atropin 1:500 produced an inhibitory effect. (Fig. XXXVIII). On a non-ganglionated horn upon which Physostigmin 1:1,550 (Figs. XXX and LI) and again 1:775 had produced an inhibitory effect, Atropin 1:500 intensified this inhibition (Fig. XXX). On the pregnant uterus of the guineapig Atropin 1:830 produced an inhibitory effect on a horn already treated with Physostigmin 1:4,600 which had caused an augmentory reaction. (Fig. LII).

This agrees with the work of Cushny (119) on the non-pregnant and

pregnant/

pregnant cat's uterus, who found that the augmentory effect of Physostigmin was completely antagonised by Atropin.

In the non-pregnant rat, Physostigmin 1:4,000 produced an increase in tone of a strip already treated with Atropin 1:1,000. This finding supports the work of Fardon,(95) who, working on the uterus of the cat, bitch, guineapig and rabbit, reported that Physostigmin produced augmentation after Atropin, and "was not apparently influenced by Atropin." Atropin, in dilutions which produce an inhibitory effect only in some cases - in others producing augmentation - after Physostigmin produced marked inhibition. In the uterus, Atropin seems to do more than remove certain abnormal forms of contraction,- as Cushny(94) considered it does in the intestine - producing complete inhibition after Physostigmin.

The results suggest that Physostigmin has some synergic action upon the uterus which renders it more susceptible to the action of Atropin, making its reaction that which is normally produced by very strong solutions of Atropin.

The action of Physostigmin in increasing the augmentor effect produced by Atropin is what was to be expected if Physostigmin acts peripherally to Atropin.

(3) Atropin and Ergotamin.

In the guineapig Atropin increased the augmentor effect already produced by Ergotamin and caused the onset of almost tonic contraction - a summation of actions.

The influence of drugs upon the rhythmic contractions

and/

and relaxations manifested by the excised uterus of the rat and the guineapig seems to indicate that these movements may be modified by an action at two or possibly three levels on the neuromuscular chain.

Nicotin, which is not antagonised by any of the others, and which does not antagonise any of them, appears to first stimulate and then depress a proximal part. Previous work upon this substance (Nicotin) indicates that this is probably the neuron cell itself.

Barium and Adrenalin appear to act on the most peripheral part: Barium on the contractile substance to stimulate: and Adrenalin, either directly upon this or upon some element just above this level, to bring about inhibition. Atropin does not act at this level. Eserin and possibly Pilocarpin are antagonised by and antagonise Adrenalin, but are themselves antagonised by Atropin. Their action seems therefore to be at some point above this capable of controlling the activity of the more peripheral mechanism. (Fig.LV).

Apart from the increased inhibitory influence of a given dose of Adrenalin, after the augmentor neuroneswere thrown out of action by Ergotoxin, there is no indication of the existence of a separate peripheral augmentor and inhibitor mechanism. The antagonism of Adrenalin and Eserin is explainable by their action on a common receptor substance.

V. SUMMARY OF RESULTS AND CONCLUSIONS.

(1) In the rat, guineapig, mouse, and human subject, the sympathetic nerve fibres supplying the uterus and vagina pass down the hypogastric nerves to the level of the cervix and then pass to the tubes, uterus, cervix, and upper portion of the vagina by several branches. These branches are intimately associated with branches of the uterine artery.

(2) Nerve cells are scattered along the hypogastric nerves and are especially numerous on the course of the hypogastric plexus opposite the cervix. On each side they form a ganglion - the cervical ganglion - which is largest and is most circumscribed in the rat and least so in the mouse.

(3) Within the wall of the genital tract, no cells have been found comparable in size, shape or staining reaction to the nerve cells found on the more proximal portions of the sympathetic nerve fibres.

(4) The rate of the contractions occurring in portions of muscle removed from the ovarian end is greater than in portions from the vaginal end of the uterine horn.

(5) A comparison of the action of uterine horns connected and not connected with the cervical ganglion, shows the absence of any effect on removal of the ganglion, and the absence of any difference in the response of the uterus with and without the ganglion to various chemical substances. These facts lead to the conclusion that the ganglion does not exercise a direct influence in/

in controlling the tone and movements of the excised uterus.

(6) The point of origin of the impulse controlling the tone and movements of the uterus appears to be within the uterine substance itself.

(7) A study of the action of drugs and their antagonism indicates that in the uterine wall there is some arrangement for the control of tone and movement, and that this may be divided into three levels:- (a) a proximal, (b) an intermediate, and (c) a peripheral level.

Apart from a slightly increased inhibitory effect produced by a given dose of Adrenalin after treatment of the uterine strip with Ergotoxin, no evidence of separate augmentor and inhibitor arrangements was demonstrated.

VI. DESCRIPTION OF ILLUSTRATIONS.

FIGURE I. Referred to on p.10.

To show the three possible forms of the terminal neurones.

A. The common efferent path:

B. Separate augmentor (+) and inhibitor (-) efferent paths acting upon a common receptor substance r and

C. Separate augmentor (+) and inhibitor (-) paths each acting upon a special receptor substance,

s. cell station.
n. nerve ending.
r. receptor substance.
c. contractile substance.
+ augmentor) nerve fibres in the hypogastric
- inhibitor) nerve.

FIGURE II. Referred to on p.12.

Dissection of aortic, inferior mesenteric nerve plexuses and hypogastric nerves in the Rat.

B. bladder.
D. descending aorta.
C.V. inferior vena cava.
H.N. hypogastric nerve.
H.U. uterine horn.
I.M. inferior mesenteric artery.
O.A. ovarian artery.
R. intestine.
U.A. uterine artery.
Ur. ureter.
V. vagina.
V.A. vesical artery.

FIGURE III. p.12.

Dissection of aortic, inferior mesenteric nerve plexuses and hypogastric nerves in the Guineapig.

B. bladder.
D. descending aorta.
H.N. hypogastric nerve.
H.U. uterine horn.
I.M. inferior mesenteric artery.
M.S. middle sacral artery.
O. ovary.
O.A. ovarian artery.
R. rectum.
R.A. renal artery.
U.A. uterine artery.
Ur. ureter.
V. vagina.
V.A. vesical artery.

FIGURE IV. p.12.

Dissection of hypogastric plexuses in the Guineapig.

B. bladder.
D. descending aorta.
H.N. hypogastric nerve.
H.U. uterine horn.
L.A. lumbar artery.
L.S. lumbo-sacral nerve trunk.
S.i, S.ii, S.iii) first, second and third sacral nerves.
U.A. uterine artery.
Ur. ureter.
V. vagina.

FIGURE V. p.14.

Diagram of part of a longitudinal section (no.64) of the genital organs of the new-born Rat, to show the position G_{Δ} of nerve cells in relation to the cervix C, uterus U and vagina V.

FIGURE VI. p.14.

Diagram from the reconstruction (posterior view) of the pelvic organs in the adult Rat, showing

C. cervix.
G.△ position of nerve cells.
H.U. uterine horn.
I.I. internal iliac artery.
U.A. uterine artery.
Ur. ureter.
V. vagina.
V.A. vesical artery.

FIGURE VII. p.16.

Foetal Guineapig - 60 days.

Diagram of Reconstruction (sections 1449-1595), as seen from the cranial aspect.

c.i. common iliac artery.
e.i. external iliac artery.
g.△ position of nerve cells.
h.n. hypogastric nerve.
h.u. uterine horn.
i.i. internal iliac artery.
i.i.a. anterior division internal iliac artery.
r. rectum.
r.a. artery to the rectum.
u.a. uterine artery.
u.n. uterine nerve.
ur. ureter.

FIGURE VIII. p.16.

Foetal Guineapig - 60 days.

Diagram of Reconstruction (Sections 1252-1449), as seen from the cranial aspect.

b.	bladder.
g.$\triangle$	position of nerve cells.
h.n.	hypogastric nerve.
i.i.	internal iliac artery.
i.i.a.	anterior division internal iliac artery.
r.	rectum.
r.a.	artery to the rectum.
r.n.	nerve to the rectum.
u.	uterus.
u.n.	uterine nerve.
ur.	ureter.

FIGURE IX. p.17.

Foetal Guineapig - 60 days.

Diagram of Reconstruction (Sections 1032-1252), as seen from the cranial aspect.

b.	bladder.
b.n.	nerve to the bladder.
g.$\triangle$	position of nerve cells.
r.	rectum.
r.a.	artery to the rectum.
r.n.	nerve to the rectum.
umb.	umbilical artery.
ur.	ureter.
v.	vagina.
v.a.	vaginal artery.

FIGURE X. p.16.

Foetal Guineapig 60 days.

Graphical Reconstruction of the nerves and arteries to the Uterus and Vagina - (Sections 1126-1745).

b.n.	nerve to the bladder.
c.i.	common iliac artery.
e.i.	external iliac artery.
h.n.	hypogastric nerve.
i.i.a.	anterior division internal iliac artery.
g.△	position of nerve cells.
r.a.	artery to the rectum.
r.n.	nerve to the rectum.
u.a.	uterine artery.
u.n.	uterine nerve.
v.a.	vaginal artery.

FIGURE XI. p.18.

Mouse. Diagram of reconstruction (Sections 647-785), as seen from the caudal aspect.

B.	bladder.
C.	cervix.
G.△	position of nerve cells.
H.N.	hypogastric nerve.
R.	rectum.
U.A.	uterine artery.
U.	urethra.
Ur.	ureter.
V.	vagina.
V.A.	vesical artery.

FIGURE XII. p.22.

Human Female Foetus of 15 cm. Length.

Drawing of upper part of block while in xylol.

b.	bladder.	t.	Fallopian tube.
o.	ovary.	ur.	ureter.
r.	rectum.	ut.	uterus.
		v.	bloodvessels.

FIGURE XIII. p.31.

Human Female Foetus of 15 cm. Length.

Flat reconstruction of the genital tract from the serial sections. For description see text.

The levels from which Figure XIV (A, B, C) are taken are indicated.

FIGURE XIV. A. p.27.

Human Female Foetus of 15 cm. Length.

Transverse section no.871:
for level see Fig. XIII.

b.	bladder.
c.	cervix.
c.i.	common iliac artery.
d.	Gartner's duct.
g.	ganglionic nerve cell.
h.n.	hypogastric nerve.
m.	striped muscle.
n.	nerve bundle.
r.	rectum.
t.	Fallopian tube.
ut.	body of uterus.
ur.	ureter.
v.	vagina.

FIGURE XIV. B and C. p.29.

Human Female Foetus of 15 cm. Length.

B. Transverse section no.1159:
for level see Fig. XIII.
C. Transverse section no.1486:
for level see Fig. XIII.

b.	bladder.	n.	nerve bundle.
c.	cervix.	r.	rectum.
c.i.	common iliac artery.	t.	Fallopian tube.
d.	Gartner's duct.	ut.	body of the uterus.
g.	ganglionic nerve cell.	ur.	ureter.
h.n.	hypogastric nerve.	v.	vagina.
m.	striped muscle.		

FIGURE XV. p.33.

Human Female Foetus of 15 cm. Length.

Flat reconstruction of the nerves from the serial sections.

a.p.	aortic plexus.
c.	cervix.
d.	Gartner's duct.
g.	position of ganglionic nerve cell.
h.n.	hypogastric nerve.
o.	nerve to the ovary.
v.	vagina.

FIGURE XVI. p.37.

Apparatus for recording uterine contractions.

O. inlet for oxygen.

FIGURE XVII. pp. 41,42.

Non-pregnant Uterus - Rat (170 grms).

Comparison between the contractions of

(A) the whole horn - 1.2" long,
(B) the ovarian end - 0.75" long, and
(C) the vaginal end of the horn - 0.3" long,

all three being unattached to the cervical ganglion.

FIGURE XVIII. pp. 41,42.

Non-pregnant Uterus - Rat (170 grms).

Comparison between the contractions of

(A) the whole horn attached to the cervix and the ganglion - 1.2" long,
(B) the ovarian end - 0.75" long,
and (C) the uterine end of the horn - 0.3" long,

(B) and (C) being unattached to the cervix and the ganglion.

FIGURE XIX. pp. 41, 42.

Non-pregnant Uterus - Rat (118 grms).

Comparison between the contractions of

(A) the uterine end -0.9" long,
(B) the ovarian end attached to the cervix and the ganglion -0.7" long,

and (C) the ovarian end of the horn -0.7" long,

(A) and (C) being unattached to the cervix and the ganglion.

FIGURE XX. p.45.

Non-pregnant Uterus - Rat (210 grms).

Comparison between the contractions of (H) the non-ganglionated - 1" long - and (G) the ganglionated horn - 1" long - before -AO and after -OB removal of the cervical ganglion. (At O when the portion carrying the ganglion was removed from the portion (G) to equalise the trauma the lower free end of portion (H) was cut away.

FIGURE XXI. p.45.

Non-pregnant Uterus - Rat (200 grms).

Comparison between the contractions of (H) the non-ganglionated - 1" long - and (G) the ganglionated horn - 1" long - before -AO and after -OB removal of the cervical ganglion. (At O when the portion carrying the ganglion was removed from the strip (G) to equalise the trauma the lower free end of the strip (H) was cut away.

FIGURE XXII. p.72.

Non-pregnant Uterus - Rat (110 grms).

Comparison between the effects of Barium chloride on

(A) the ganglionated - 1.9" long, and

(B) the non-ganglionated horn - 2.1" long.

FIGURE XXIII. pp. 67, 75.

Non-pregnant Uterus - Guineapig (525 grms).

The effect of Adrenalin 1:200,000 after Barium chloride 1:2,500 upon the non-ganglionated horn.

FIGURE XXIV. pp. 55, 72.

Non-pregnant Uterus - Rat (195 grms).

Comparison between the effect of Adrenalin 1:166,700 upon a portion

(A) comprising the uterine end of the horn and the cervix carrying the ganglion.

(B) comprising the ovarian end of the horn unattached to the ganglion.

FIGURE XXV. p.55.

Non-pregnant Uterus - Rat (160 grms).

The effect of Adrenalin 1:40,000,000 upon the ganglionated horn - 1.6" long.

FIGURE XXVI. p.58.

Non-pregnant Uterus - Rat (180 grms).

Comparison between the effect of Pilocarpin nitrate 1:2,500 on

(A) the non-ganglionated horn - 0.5" long,

and (B) the ganglionated horn - 0.8" long, each portion being from the ovarian end of the horns.

FIGURE XXVII. pp. 58, 72.

Pregnant Uterus - Rat (190 grms).

Comparison between the effect of Pilocarpin 1:2,500 on

(A) the ganglionated - $1\frac{3}{8}$" long, and

(B) the non-ganglionated horn - $1\frac{3}{4}$" long.

FIGURE XXVIII. pp. 58, 72.

Pregnant Uterus - Rat (220 grms).

Comparison between the effect of Pilocarpin 1:2,000 upon a portion

(A) comprising the uterine end of the horn and the cervix carrying with it the ganglion, and upon a portion

(B) from the ovarian end of the horn.

FIGURE XXIX. p.60.

Non-pregnant Uterus - Rat (170 grms).

Comparison between the effect of Eserin sulphate 1:1,550 on

(A) the whole horn attached to the cervix and the ganglion - 1.2" long,

(B) the ovarian end - 0.75" long, and

(C) the uterine end - 0.3" long.

FIGURE XXX. p.60.

Non-pregnant Uterus - Rat (225 grms).

The effect of Atropin 1:500 after Physostigmin 1:1,550 and secondly after Physostigmin 1:775 upon the non-ganglionated horn - 1.1" long.

FIGURE XXXI. pp. 63,73

Non-pregnant Uterus - Rat (230 grms).

Comparison between the effect of Atropin 1:1,000 on

(A) the non-ganglionated horn - $1\frac{3}{8}$" long and

(B) the ganglionated horn - $1\frac{1}{4}$" long.

FIGURE XXXII. pp. 64,73.

Non-pregnant Uterus - Guineapig (400 grms).

Comparison between the effect of Atropin 1:1,000 followed by Adrenalin 1:250,000 on

(A) the horn unattached, and

(B) the uterine end of the horn and cervix attached to the ganglion.

FIGURE XXXIII. pp. 67, 73.

Non-pregnant Uterus - Rat (190 grms).

Comparison between the effect of Nicotin 1:2,000 on two non-ganglionated portions of horn:-

(A) $1\frac{3}{4}$", and

(B) $2\frac{1}{4}$" long.

FIGURE XXXIV. p.68.

Non-pregnant Uterus - Rat (180 grms).

Comparison between the effect of Nicotin 1:1,000 upon

(A) the ganglionated horn - $2\frac{3}{4}$" long, and

(B) the non-ganglionated horn - $2^3/8$" long.

FIGURE XXXV. p.68.

Non-pregnant Uterus - Guineapig (380 grms).

Augmentory effect produced by Nicotin 1:2,500 on the non-ganglionated horn.

FIGURE XXXVI. pp. 71, 73.

Non-pregnant Uterus - Rat (160 grms).

Comparison between the effect of Ergotoxin phosphate 1:10,000,000 upon

(A) the non-ganglionated - 2.2" long, and

(B) the ganglionated horn - 1.6" long.

FIGURE XXXVII. p. 71.

Pregnant Uterus - Guineapig (590 grms).

Effect of Ergotamin tartrate 1:1,000 upon the ganglionated horn.

FIGURE XXXVIII. pp. 60, 80.

Non-pregnant Uterus - Rat (135 grms).

Comparison between the effect of Physostigmin 1:3,000 followed by Atropin 1:500 upon

(A) the non-ganglionated - $1\frac{1}{4}$" long, and

(B) the ganglionated horn - $1\frac{1}{4}$" long.

FIGURE XXXIX. p.75.

Non-pregnant Uterus - Rat (195 grms).

Effect of Barium chloride 1:1,250 after Adrenalin 1:166,700 upon a portion (0.75" long) comprising the uterine end of the horn and the cervix attached to the ganglion.

FIGURE XL. p.78.

Non-pregnant Uterus - Rat (145 grms).

Effect of Atropin 1:1,000 after Barium Chloride 1:1,000 upon

(A) the ganglionated - $1\frac{1}{2}$" long, and

(B) the non-ganglionated horn - 1" long.

FIGURE XLI. p.77.

Non-pregnant Uterus - Rat (145 grms).

(A) The effect of Nicotin 1:1,000 after Barium Chloride 1:2,500.

(B) The effect of Barium Chloride 1:2,500 after Nicotin 1:1,000,

upon the non-ganglionated horn - 1" long.

FIGURE XLII. p.77.

Non-pregnant Uterus - Rat (210 grms).

Effect of Pilocarpin 1:2,000 followed by Adrenalin 1:100,000 (injected into the bath) upon the non-ganglionated horn - 1" long.

FIGURE XLIII. p.77.

Non-pregnant Uterus - Rat (160 grms).

Effect of Adrenalin 1:100,000 after Physostigmin 1:2,500 on the non-ganglionated horn.

FIGURE XLIV. p.77.

Pregnant Uterus - Guineapig (590 grms).

Effect of Physostigmin 1:4,600 upon a strip treated with Adrenalin 1:100,000.

FIGURE XLV. pp. 63, 78.

Non-pregnant Uterus - Rat (145 grms).

Effect of Adrenalin 1:166,700 after Atropin 1:670 on the non-ganglionated horn.

FIGURE XLVI.

Non-pregnant Uterus - Rat (145 grms). pp. 68,73,78.

Comparison between the effect of Nicotin 1:1,000 followed by Adrenalin 1:400,000 upon

(A) the non-ganglionated - $1\frac{1}{4}$" long, and

(B) the ganglionated horn - $1\frac{1}{4}$" long.

FIGURE XLVII. pp. 55, 79.

Pregnant Uterus - Rat (220 grms).

Effect of Ergotamin tartrate 1:1,000 after Adrenalin 1:166,700 upon a portion comprising the uterine end of the horn and cervix carrying with it the ganglion.

FIGURE XLVIII. p.79.

Non-pregnant Uterus - Rat (160 grms).

Comparison between the effect of Adrenalin 1:50,000,000 (i) before and (ii) after treatment of

(A) the ganglionated and

(B) the non-ganglionated horn with Ergotoxin phosphate 1:2,500,000.

FIGURE XLIX. p.80.

Non-pregnant Uterus - Rat (210 grms).

The effect of Atropin 1:1,000 after Pilocarpin 1:2,000 upon the non-ganglionated horn - 1" long.

FIGURE L. p.59.

Non-pregnant Uterus - Guineapig (470 grms).

Effect of Atropin 1:1,000 after Pilocarpin 1:2,000 upon the non-ganglionated horn.

FIGURE LI. p.80.

Non-pregnant Uterus - Rat (225 grms).

The effect of Atropin 1:500 after Physostigmin 1:1550 upon the non-ganglionated horn.

FIGURE LII. pp. 60, 61, 80.

Pregnant Uterus - Guineapig (590 grms).

The effect of Atropin 1-830 after Physostigmin 1:4,600 upon the non-ganglionated horn.

FIGURE LIII. p.55.

Pregnant Uterus - Guineapig (600 grms.)

Comparison between the effect of Adrenalin 1:250,000 upon

(A) the non-ganglionated portion and

(B) the ganglionated portion comprising the uterine end of the horn and the cervix.

FIGURE LIV. p.55.

Non-pregnant Uterus - Guineapig (600 grms). Comparison between the effect of Adrenalin 1-166,700 upon

(A) a portion comprising the uterine end of the horn and cervix with the ganglion and

(B) a portion of the ovarian end of the horn unattached to the ganglion.

FIGURE LV. p.82.

Diagram showing three possible levels on the neuromuscular chain at which drugs act to modify the movements of the excised uterus.

s. nerve station.
n. nerve ending.
r. receptor substance.
c. contractile substance.
+ augmentor) fibres of the hypogastric nerve.
- inhibitor)

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VIII. ILLUSTRATIONS.

FIGURE I.

To show the three possible forms of the terminal neurones.

A. The common efferent path;

B. Separate augmentor (+) and inhibitor (-) efferent paths acting upon a common receptor substance r and

C. Separate augmentor (+) and inhibitor (-) paths each acting upon a special receptor substance,

s. cell station.
n. nerve ending.
r. receptor substance.
c. contractile substance.
+ augmentor) nerve fibres in the hypo-
- inhibitor) gastric nerve.

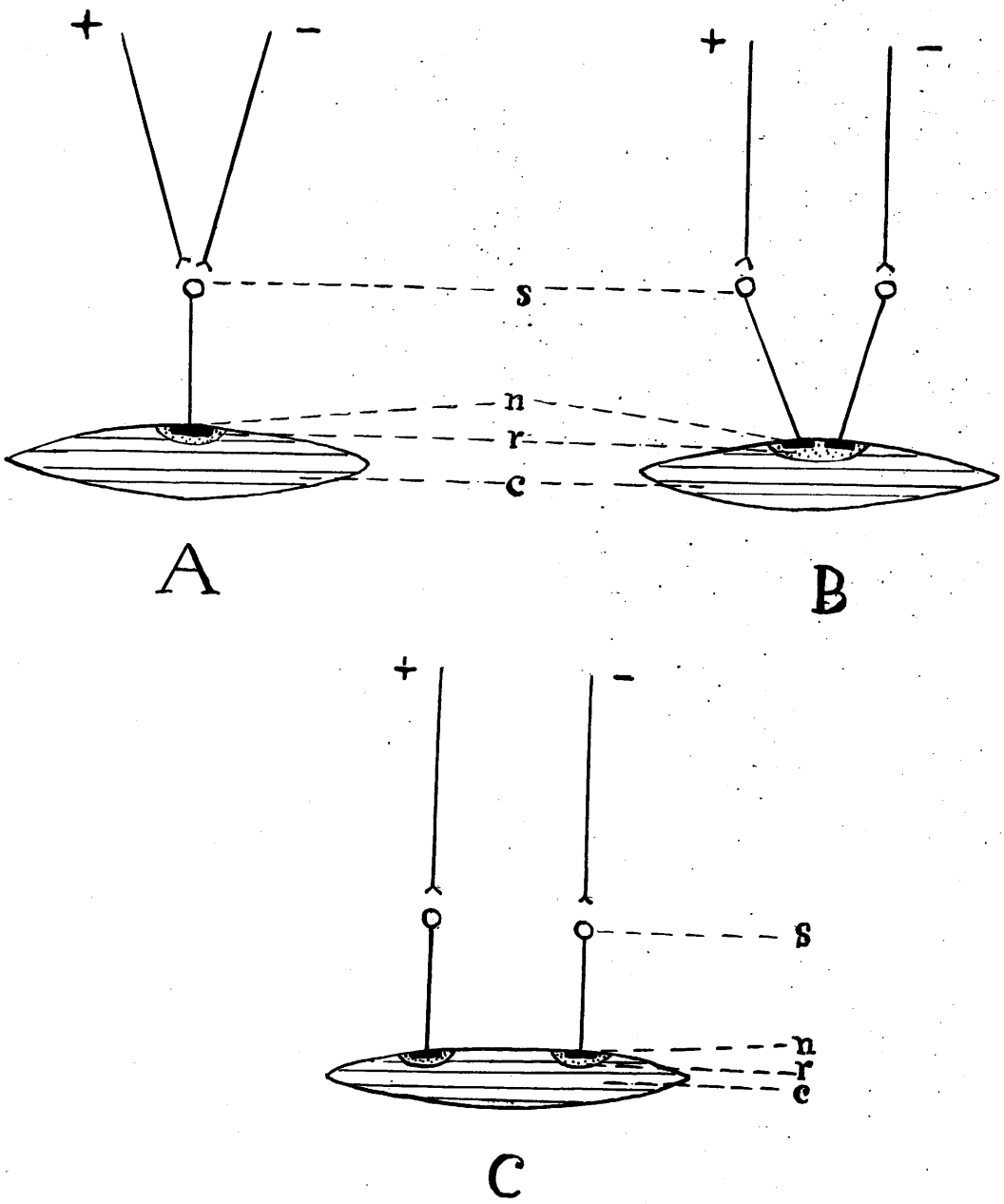

Fig I

FIGURE II.

Dissection of aortic, inferior mesenteric nerve plexuses and hypogastric nerves in the Rat.

B.	bladder.
D.	descending aorta.
C.V.	inferior vena cava.
H.N.	hypogastric nerve.
H.U.	uterine horn.
I.M.	inferior mesenteric artery.
O.A.	ovarian artery.
R.	intestine.
U.A.	uterine artery.
Ur.	ureter.
V.	vagina.
V.A.	vesical artery.

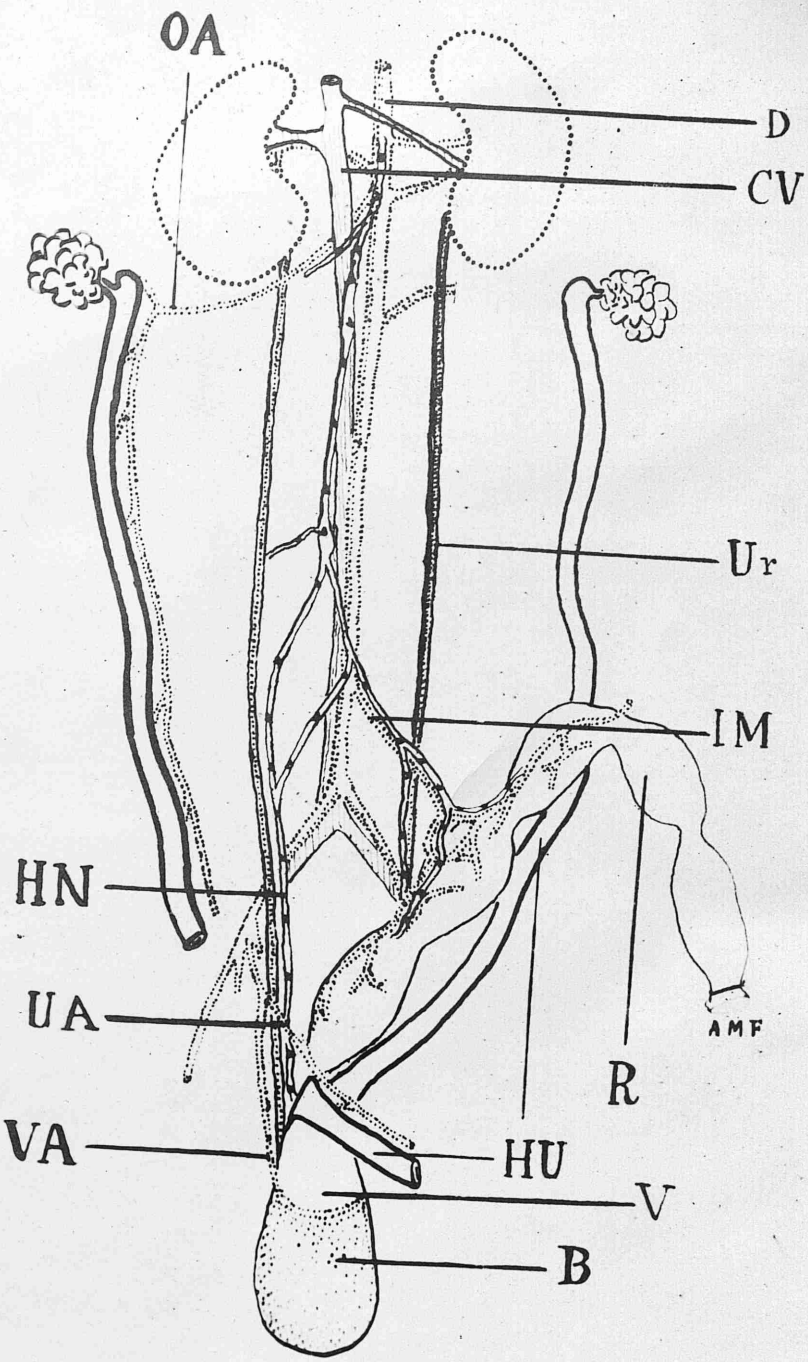

Fig. II

FIGURE III.

Dissection of aortic, inferior mesenteric nerve plexuses and hypogastric nerves in the Guineapig.

B.	bladder.
D.	descending aorta.
H.N.	hypogastric nerve.
H.U.	uterine horn.
I.M.	inferior mesenteric artery.
M.S.	middle sacral artery.
O.	ovary.
O.A.	ovarian artery.
R.	rectum.
R.A.	renal artery.
U.A.	uterine artery.
Ur.	ureter.
V.	vagina.
V.A.	vesical artery.

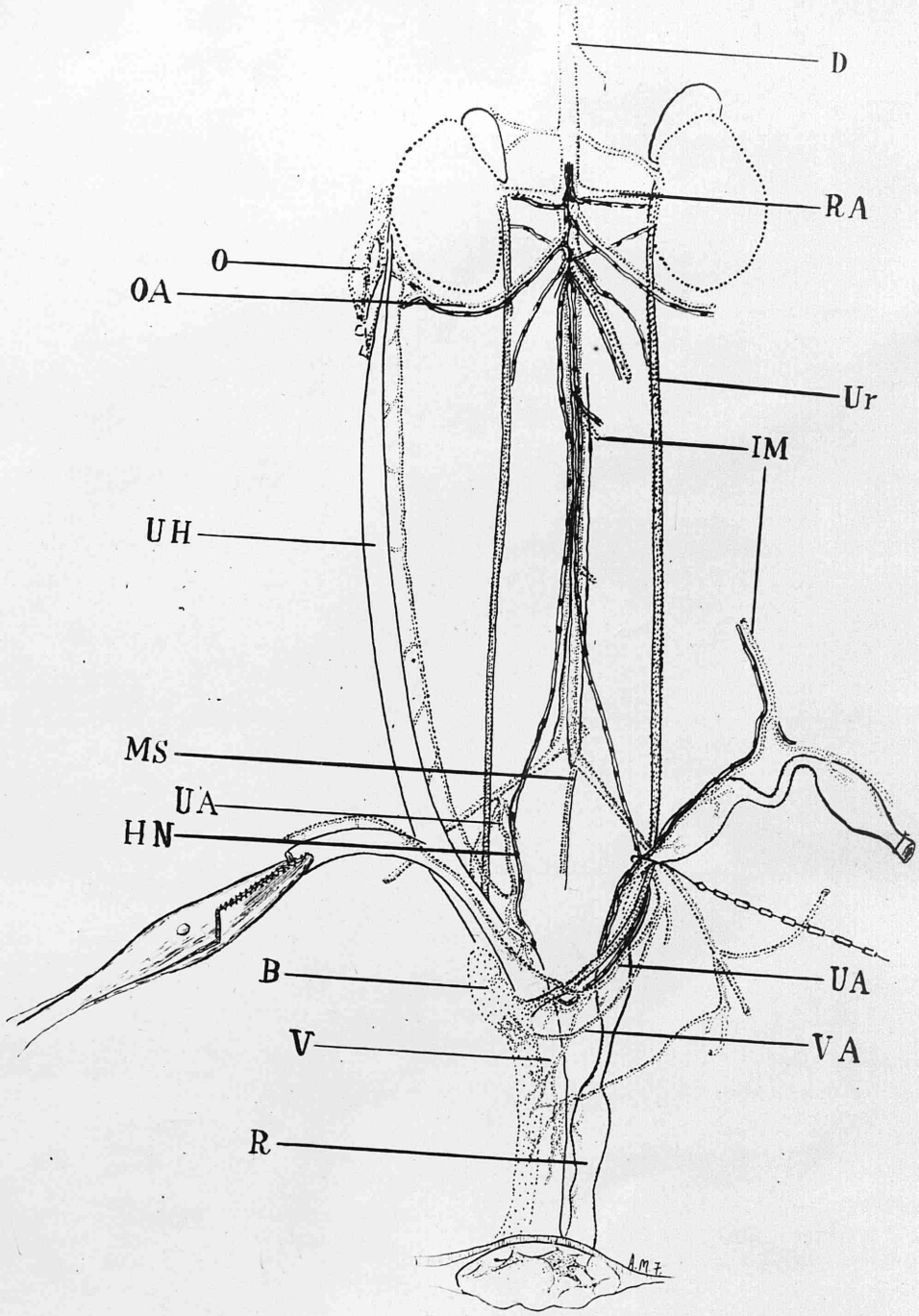

Fig III

FIGURE IV.

Dissection of hypogastric plexuses in the Guineapig.

B. bladder.
D. descending aorta.
H.N. hypogastric nerve.
H.U. uterine horn.
L.A. lumbar artery.
L.S. lumbo-sacral nerve trunk.
S.i)
S.ii) first, second and third
S.iii) sacral nerves.
U.A. uterine artery.
Ur. ureter.
V. vagina.

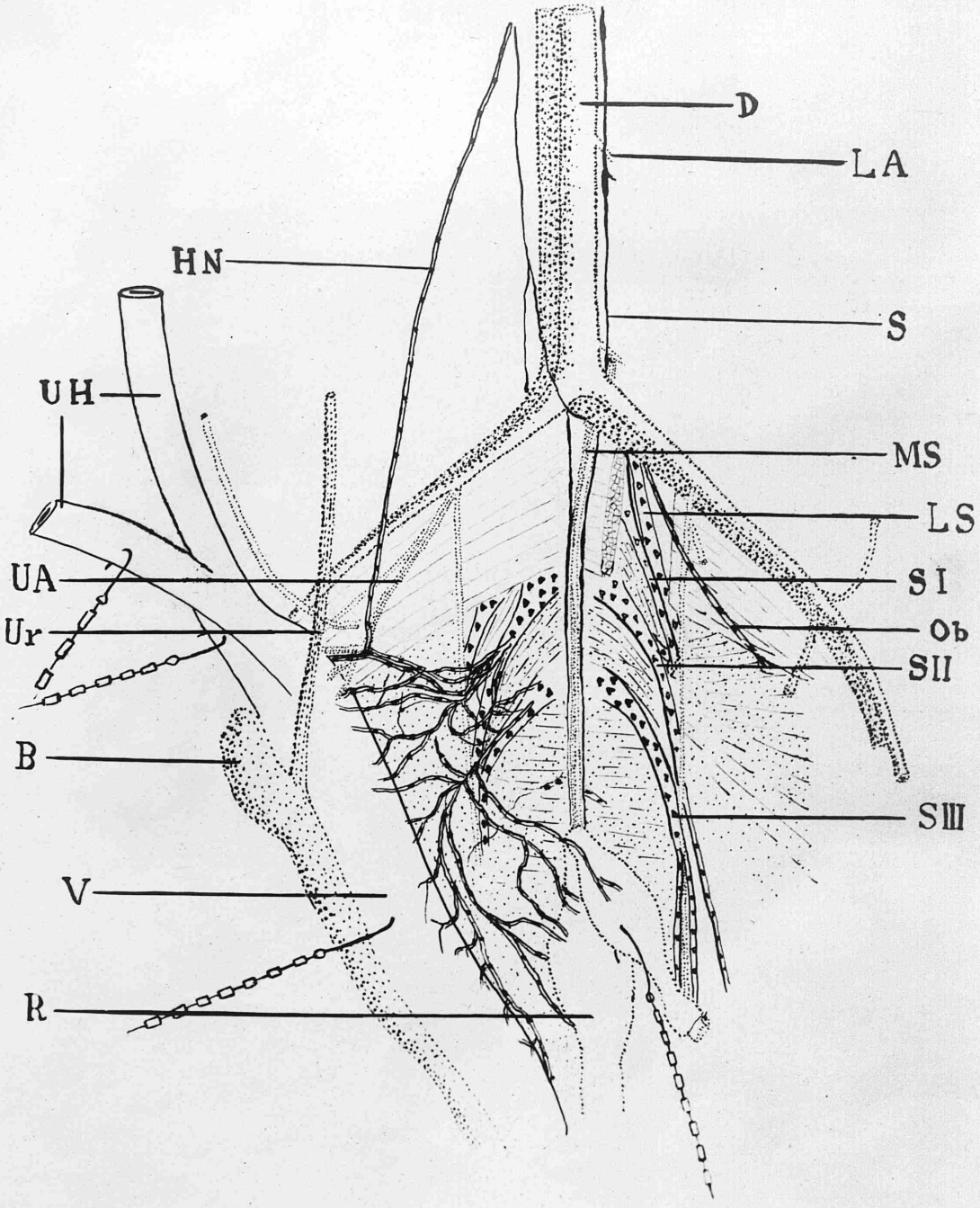

Fig IV

FIGURE V.

Diagram of part of a longitudinal section (no.64) of the genital organs of the new-born Rat, to show the position G^A of nerve cells in relation to the cervix C, uterus U and vagina V.

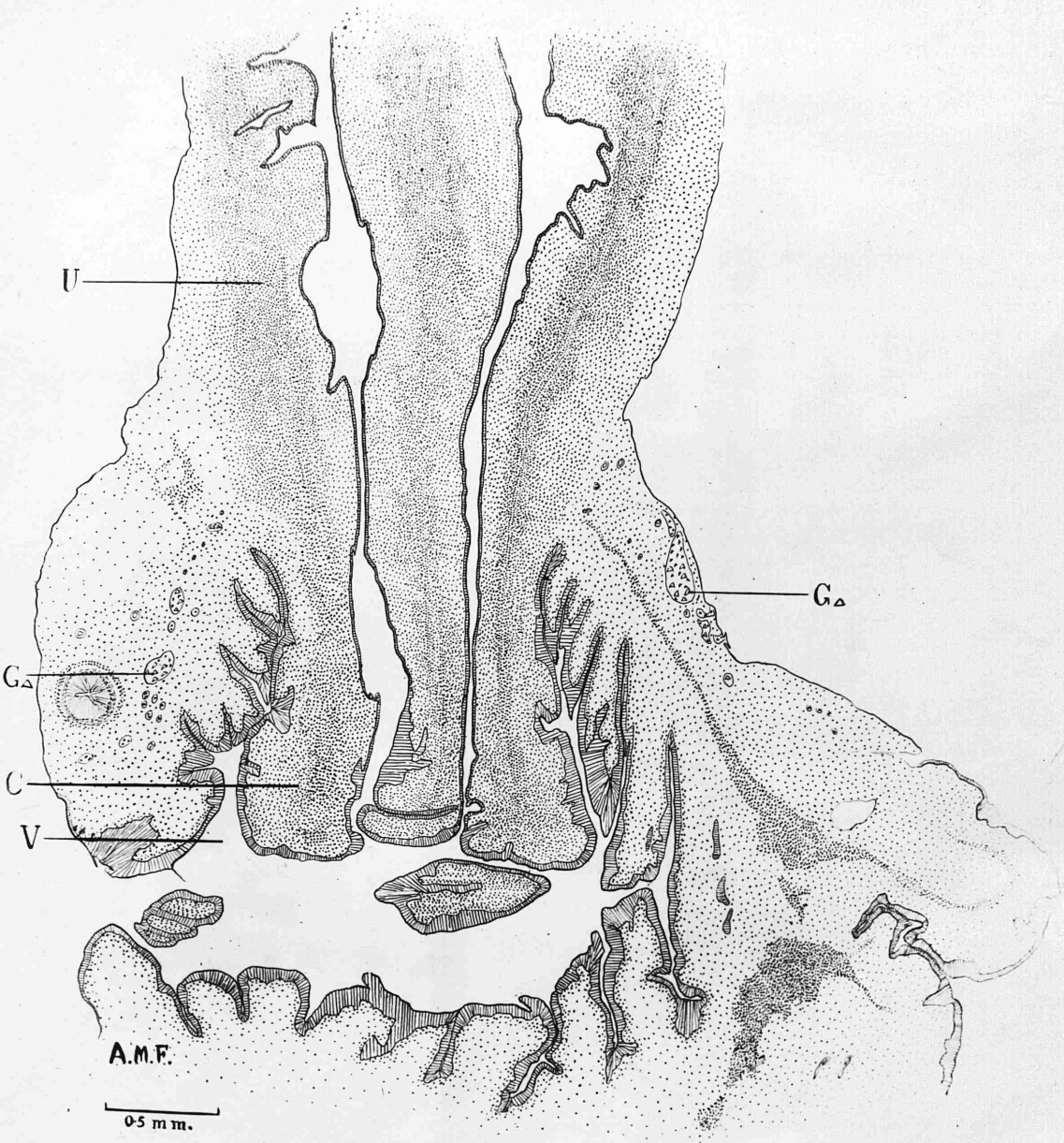

Fig. V

FIGURE VI.

Diagram from the reconstruction (posterior view) of the pelvic organs in the adult Rat, showing

C. cervix.
G.A. position of nerve cells.
H.U. uterine horn.
I.I. internal iliac artery.
U.A. uterine artery.
Ur. ureter.
V. vagina.
V.A. vesical artery.

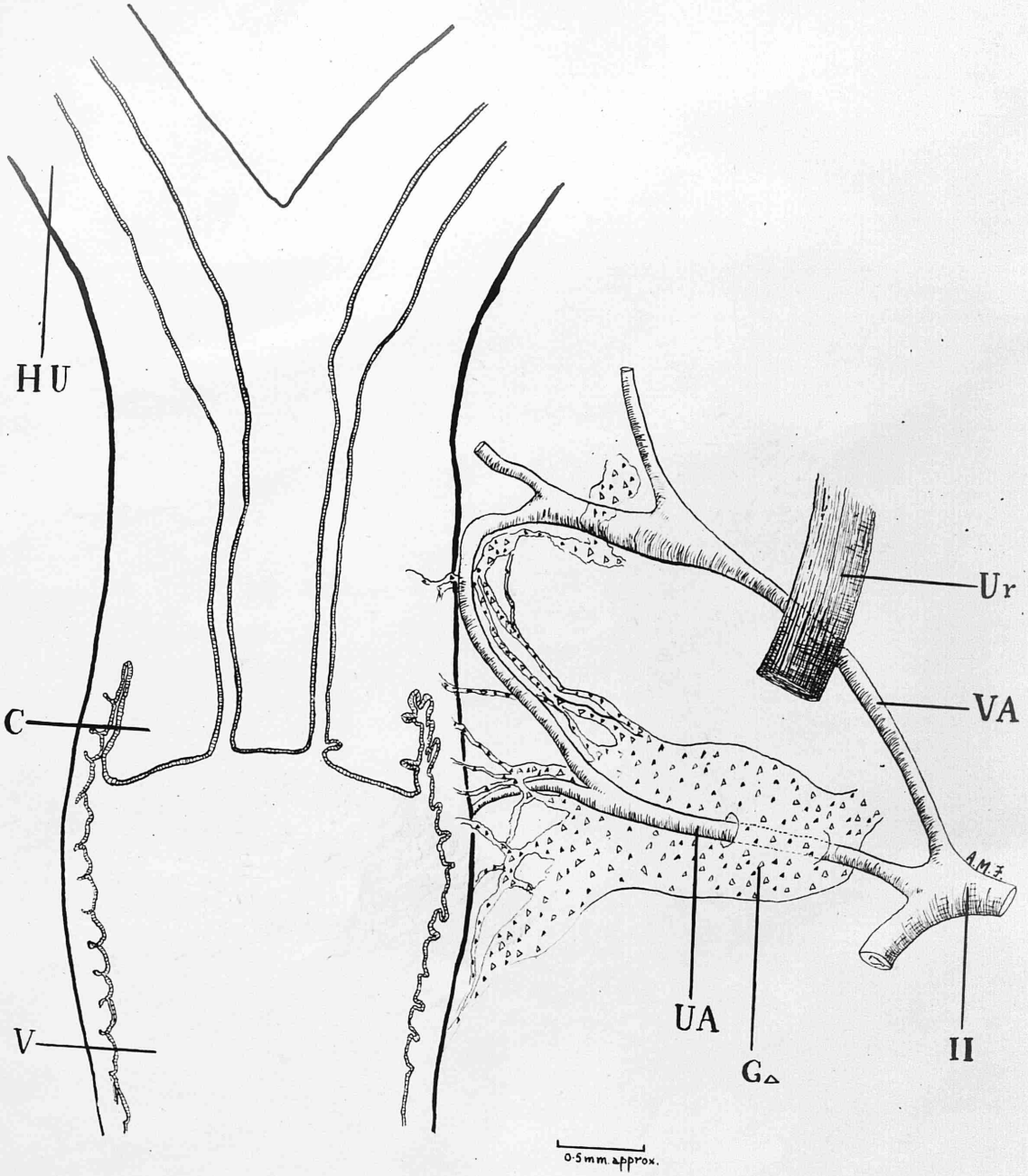

Fig VI

FIGURE VII.

Foetal Guineapig - 60 days.

Diagram of Reconstruction (sections 1449-1595), as seen from the cranial aspect.

c.i. common iliac artery.
e.i. external iliac artery.
g.△ position of nerve cells.
h.n. hypogastric nerve.
h.u. uterine horn.
i.i. internal iliac artery.
i.i.a. anterior division internal iliac artery.
r. rectum.
r.a. artery to the rectum.
u.a. uterine artery.
u.n. uterine nerve.
ur. ureter.

Fig VII

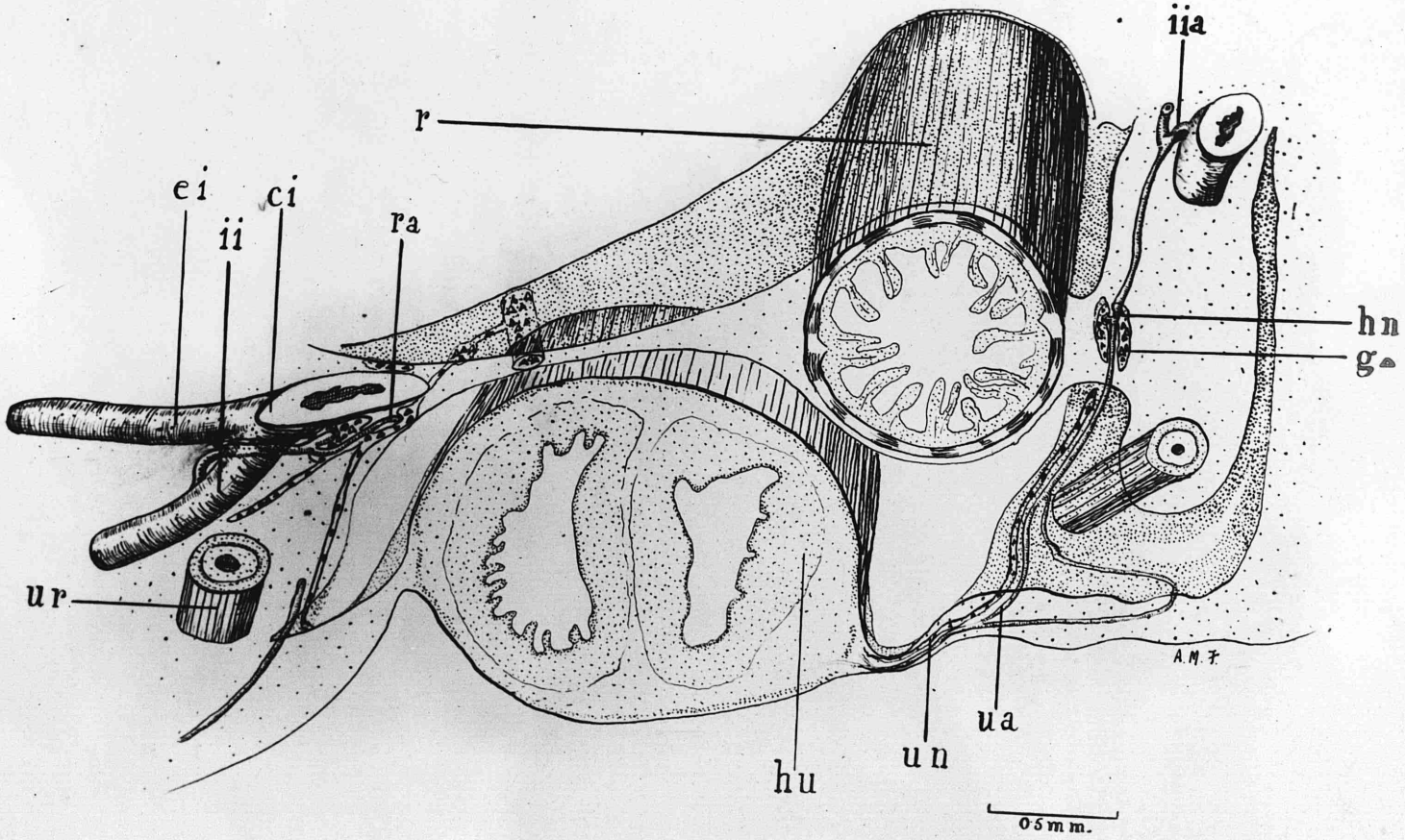

FIGURE VIII.

Foetal Guineapig - 60 days.

Diagram of Reconstruction (Sections 1252-1449), as seen from the cranial aspect.

b. bladder.
g.Δ. position of nerve cells.
h.n. hypogastric nerve.
i.i. internal iliac artery.
i.i.a. anterior division internal iliac artery.
r. rectum.
r.a. artery to the rectum.
r.n. nerve to the rectum.
u. uterus.
u.n. uterine nerve.
ur. ureter.

Fig. VIII

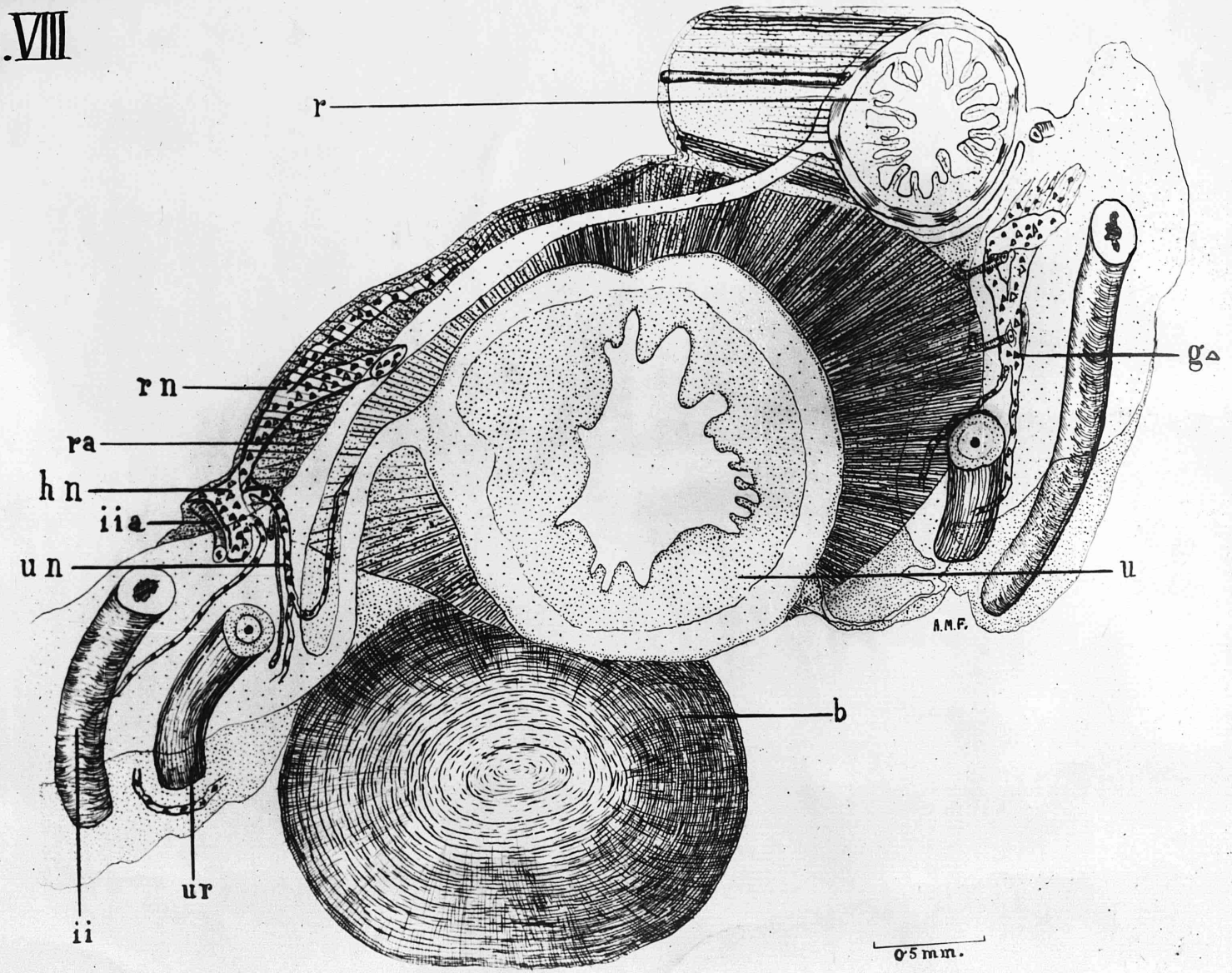

FIGURE IX.

Foetal Guineapig - 60 days.

Diagram of Reconstruction (sections 1032-1252), as seen from the cranial aspect.

b.	bladder.
b.n.	nerve to the bladder.
g.△.	position of nerve cells.
r.	rectum.
r.a.	artery to the rectum.
r.n.	nerve to the rectum.
umb.	umbilical artery.
ur.	ureter.
v.	vagina.
v.a.	vaginal artery.

Fig. IX

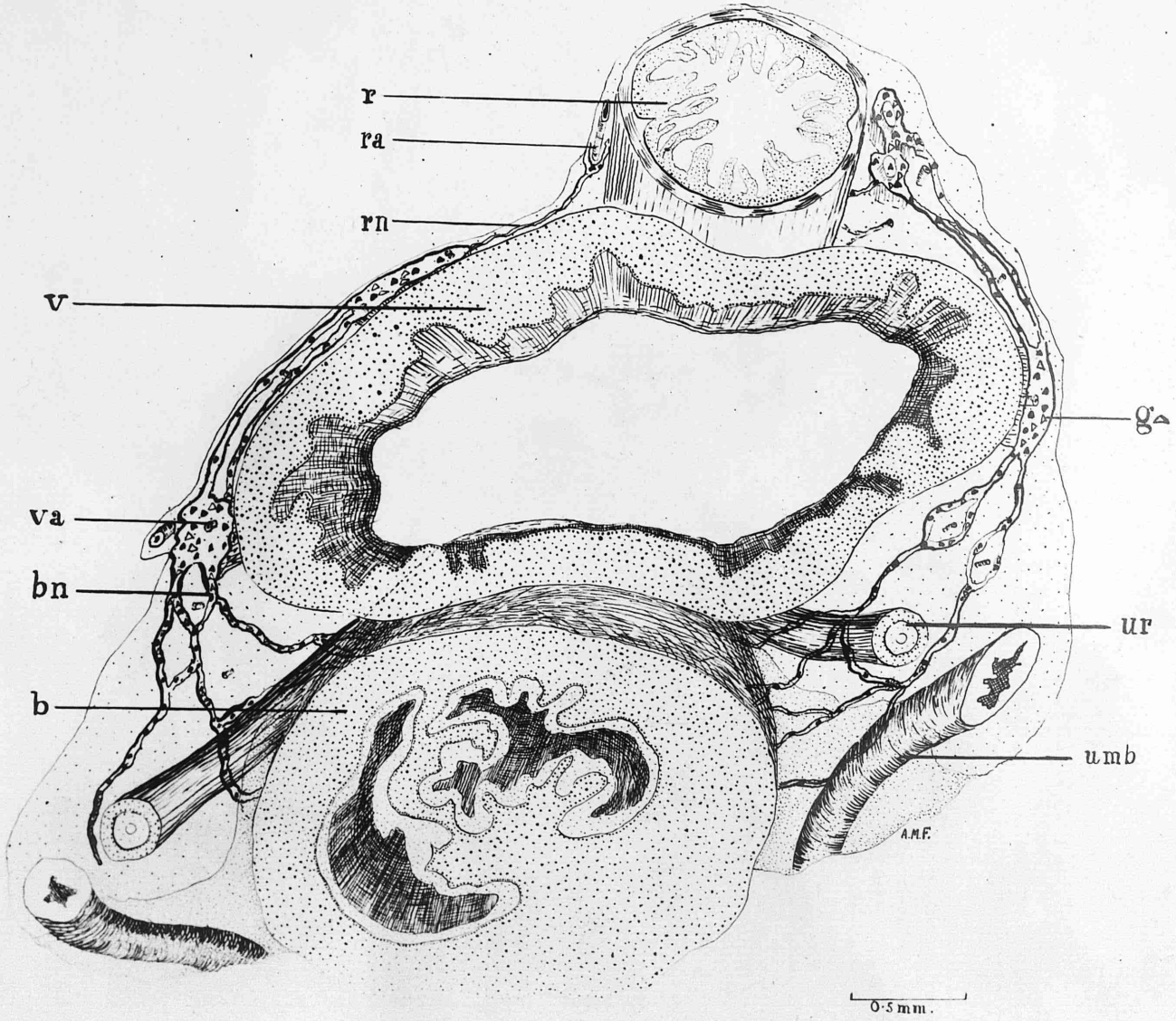

FIGURE X.

Foetal Guineapig 60 days.

Graphical Reconstruction of the nerves and arteries to the Uterus and Vagina - sections (1126-1745).

b.n.	nerve to the bladder.
c.i.	common iliac artery.
e.i.	external iliac artery.
h.n.	hypogastric nerve.
i.i.a.	anterior division internal iliac artery.
g.a.	position of nerve cells.
r.a.	artery to the rectum.
r.n.	nerve to the rectum.
u.a.	uterine artery.
u.n.	uterine nerve.
v.a.	vaginal artery.

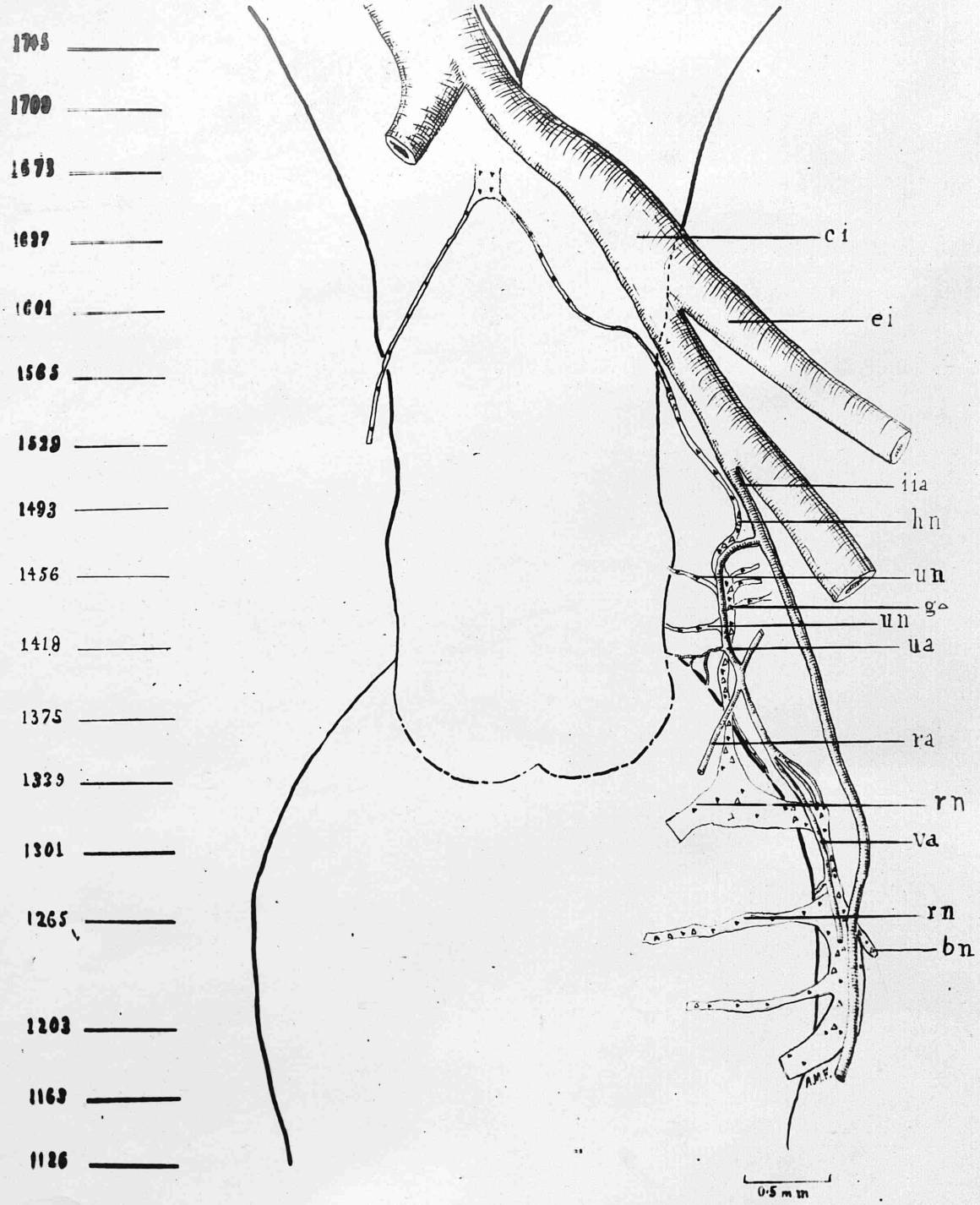
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Fig.X

FIGURE XI.

Mouse. Diagram of reconstruction (sections 647-785), as seen from the caudal aspect.

B. bladder.
C. cervix.
G.△. position of nerve cells.
H.N. hypogastric nerve.
R. rectum.
U.A. uterine artery.
U.△. urethra.
Ur. ureter.
V. vagina.
V.A. vesical artery.

Fig. XI

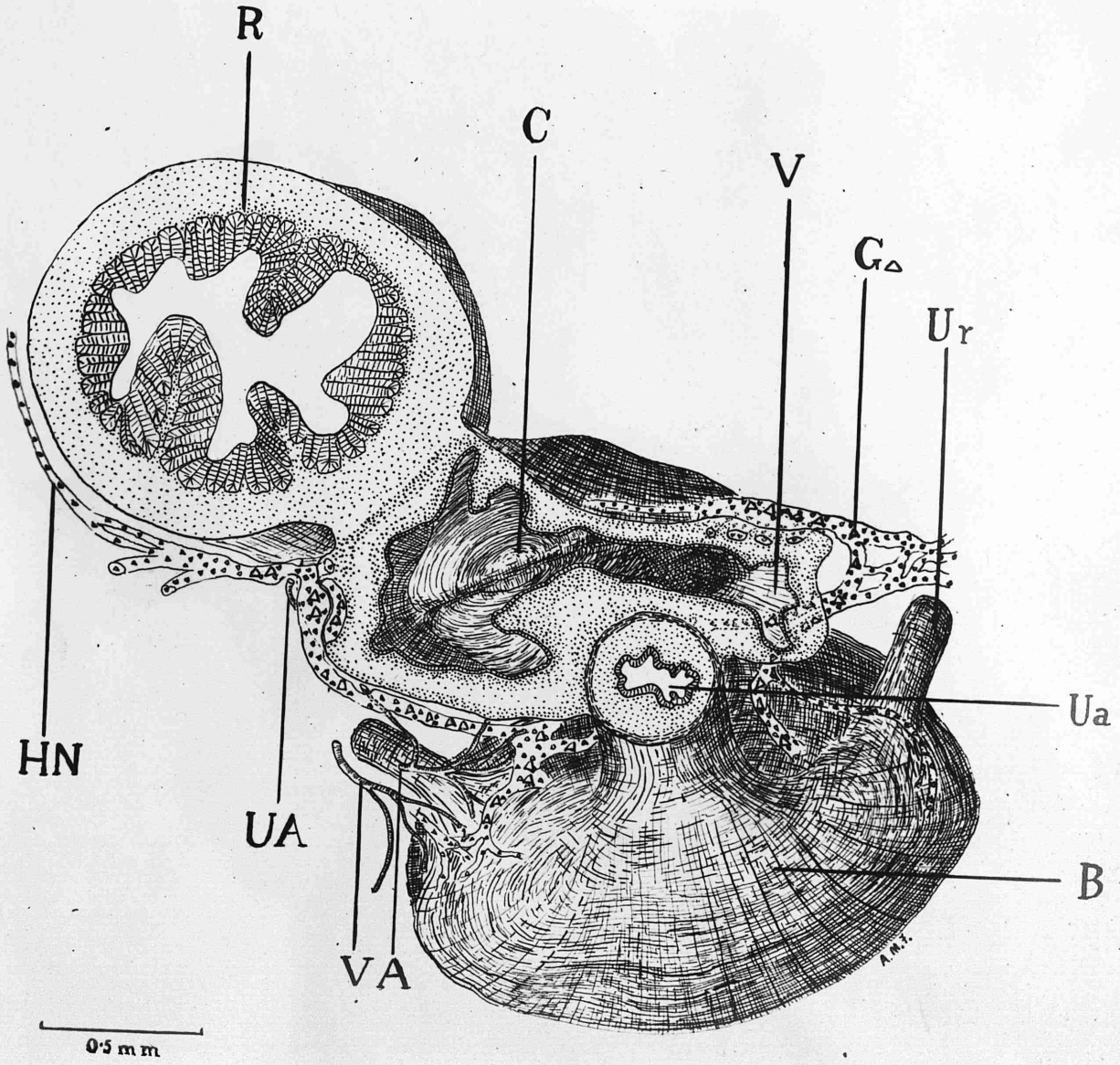


FIGURE XII.

Human Female Foetus of 15 cm. Length.

Drawing of upper part of block while in xylol.

b.	bladder.
o.	ovary.
r.	rectum.
t.	Fallopian tube.
ur.	ureter.
ut.	uterus.
v.	bloodvessels.

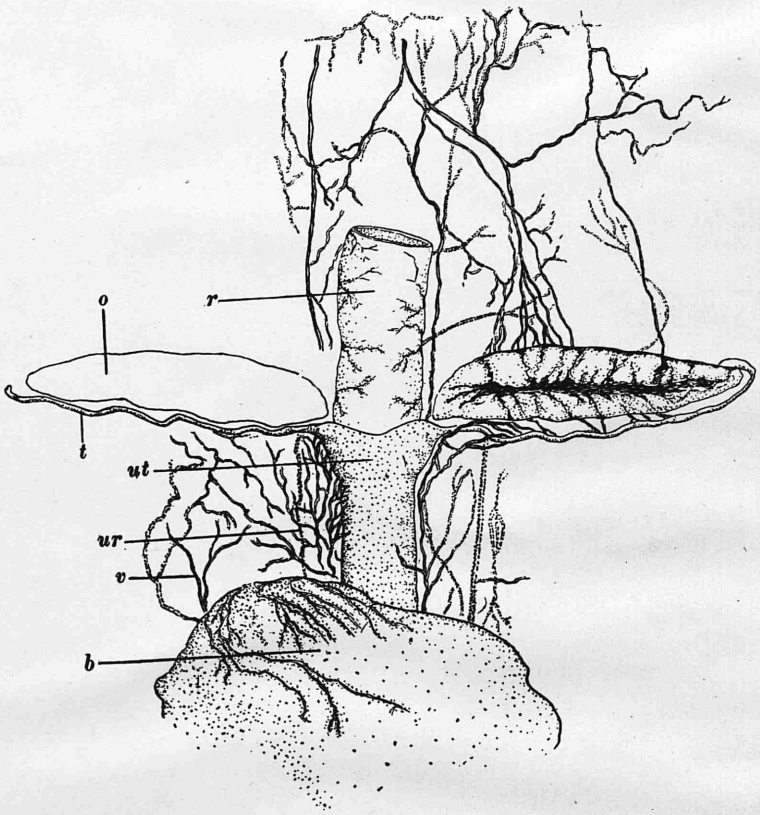


Fig XII

FIGURE XIII.

Human Female Foetus of 15 cm. Length.

Flat reconstruction of the genital tract from the serial sections. For description see text.

The levels from which Figure XIV (A, B, C) are taken are indicated.

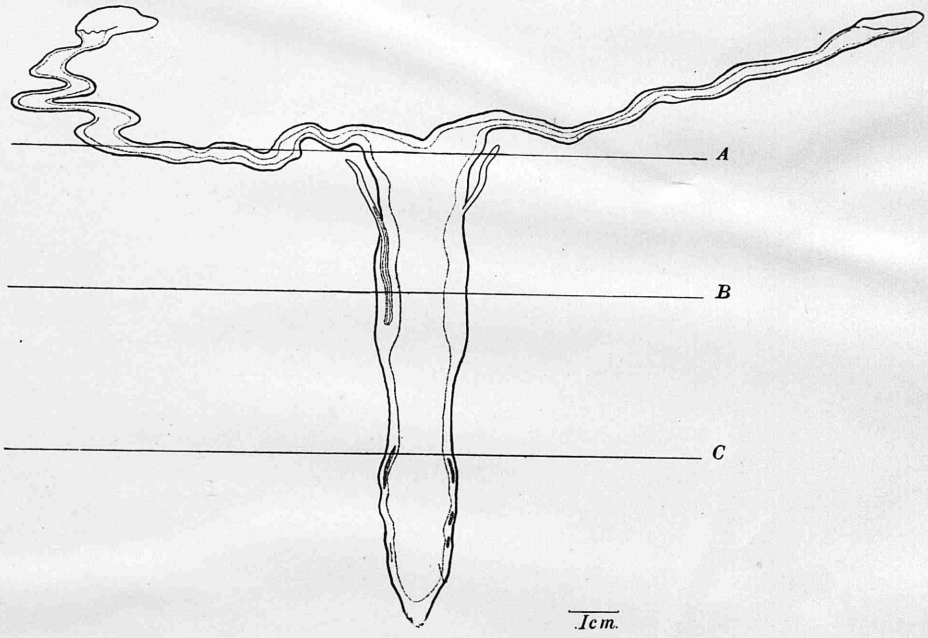


Fig. XIII

FIGURE XIV. A.

Human Female Foetus of 15 cm. Length.

Transverse section no. 871:
for level see Fig. XIII.

b.	bladder.
c.	cervix.
c.i.	common iliac artery.
d.	Gartner's duct.
g.	ganglionic nerve cell.
h.n.	hypogastric nerve.
m.	striped muscle.
n.	nerve bundle.
r.	rectum.
t.	Fallopian tube.
ut.	body of uterus.
ur.	ureter.
v.	vagina.

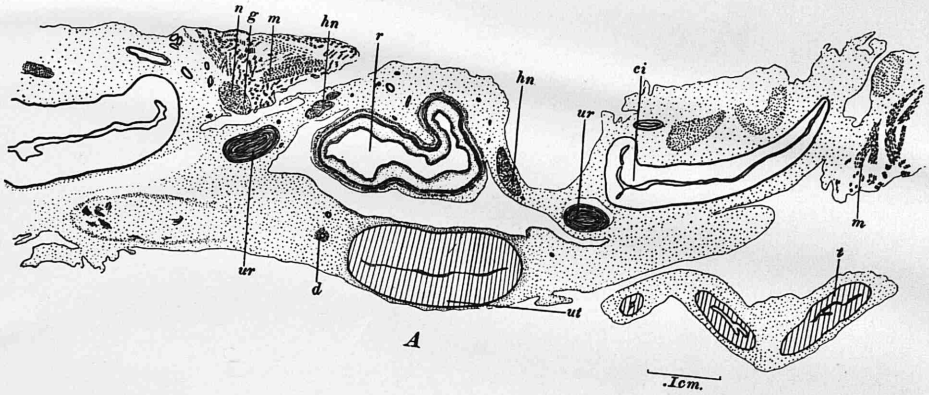


Fig. XIV

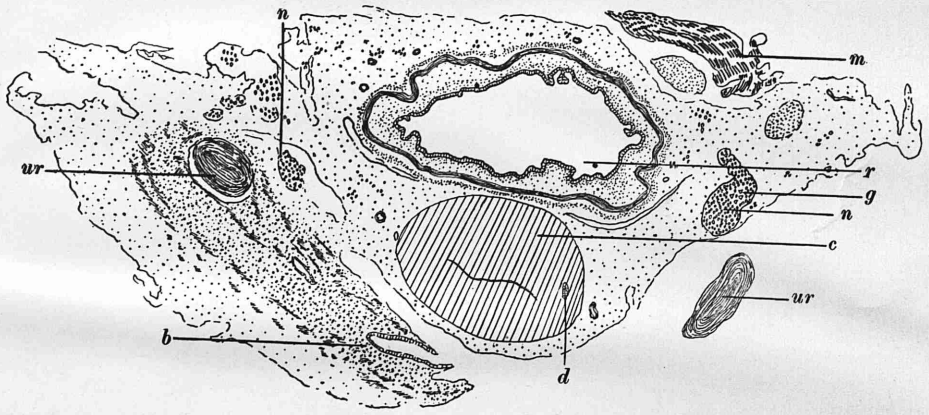
FIGURE XIV. B and C.

Human Female Foetus of 15 cm. length.

B. Transverse section no. 1159:
for level see Fig. XIII.

C. Transverse section no. 1486:
for level see Fig. XIII.

b.	bladder.
c.	cervix.
c.i.	common iliac artery.
d.	Gartner's duct.
g.	ganglionic nerve cell.
h.n.	hypogastric nerve.
m.	striped muscle.
n.	nerve bundle.
r.	rectum.
t.	Fallopian tube.
ut.	body of the uterus.
ur.	ureter.
v.	vagina.



B

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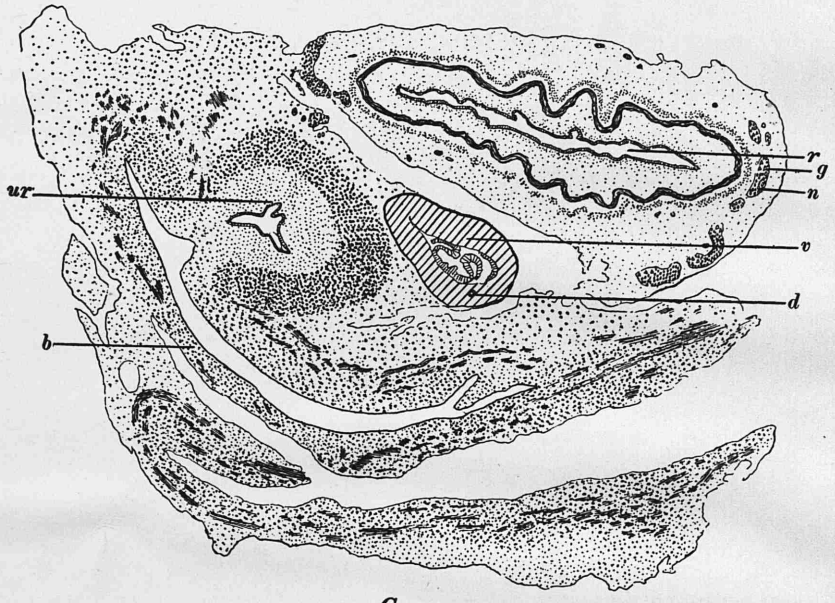


C

.1cm.

Fig. XIV

FIGURE XV.

Human Female Foetus of 15 cm. Length.

Flat reconstruction of the nerves from the serial sections.

a.p. aortic plexus.
c. cervix.
d. Gartner's duct.
g. position of ganglionic nerve cell.
h.n. hypogastric nerve.
o. nerve to the ovary.
v. vagina.

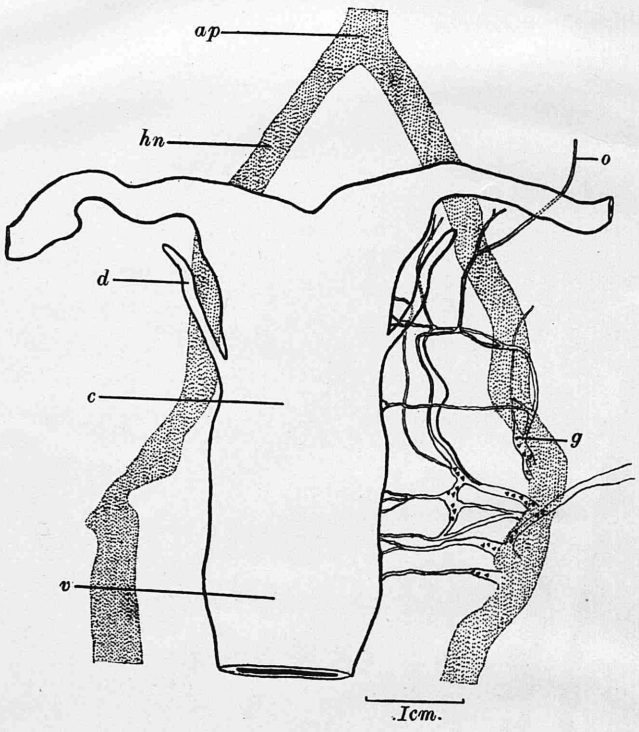


Fig. XV

FIGURE XVI.

Apparatus for recording uterine contractions.

O. inlet for oxygen.

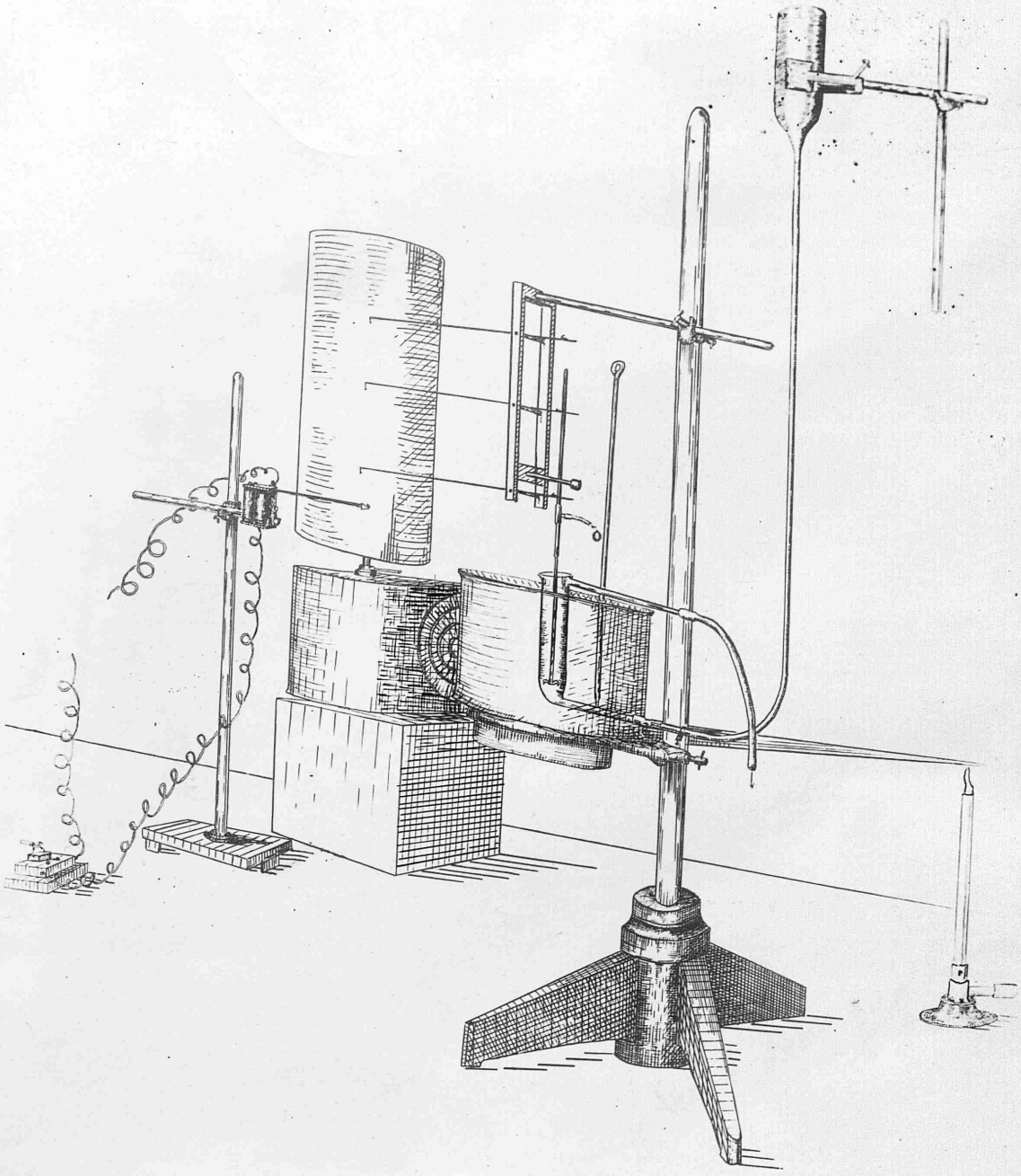


Fig. XVI

FIGURE XVII.

Non-pregnant Uterus- Rat (170 grms).

Comparison between the contractions of

(A) the whole horn - 1.2" long,

(B) the ovarian end - 0.75" long, and

(C) the vaginal end of the horn - 0.3" long,

all three being unattached to the cervical ganglion.

Fig XVII

A Whole horn attached to cervix and ganglion — 1·2".

B Ovarian end of horn (non-ganglionated) — 0·75".

C Uterine end of horn (non-ganglionated) — 0·3".

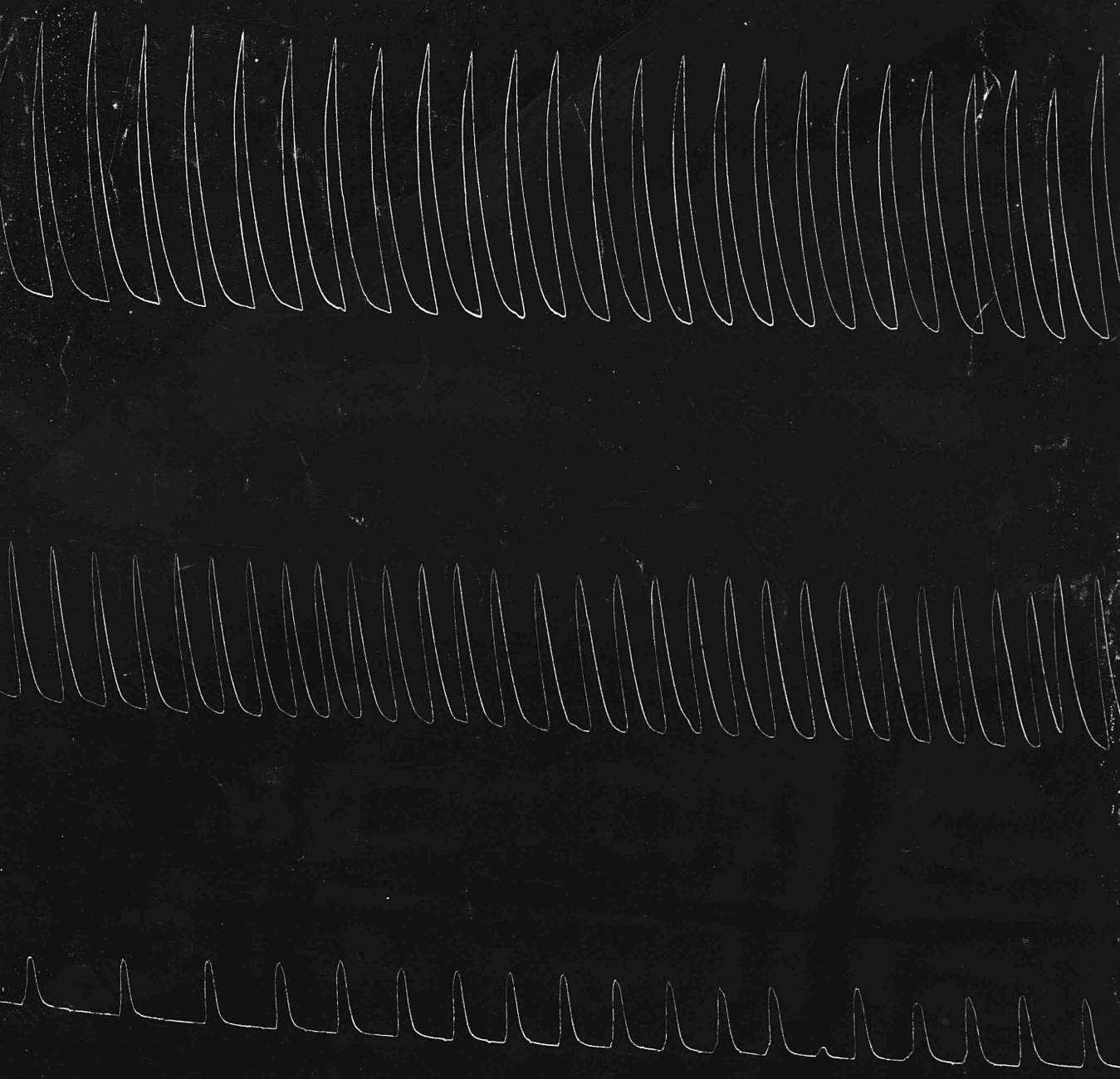


FIGURE XVIII.

Non-pregnant Uterus - Rat (170 grms).

Comparison between the contractions of

(A) the whole horn attached to the cervix and the ganglion - 1.2" long,

(B) the ovarian end - 0.75" long,

and (C) the uterine end of the horn - 0.3" long,

(B) and (C) being unattached to the cervix and the ganglion.

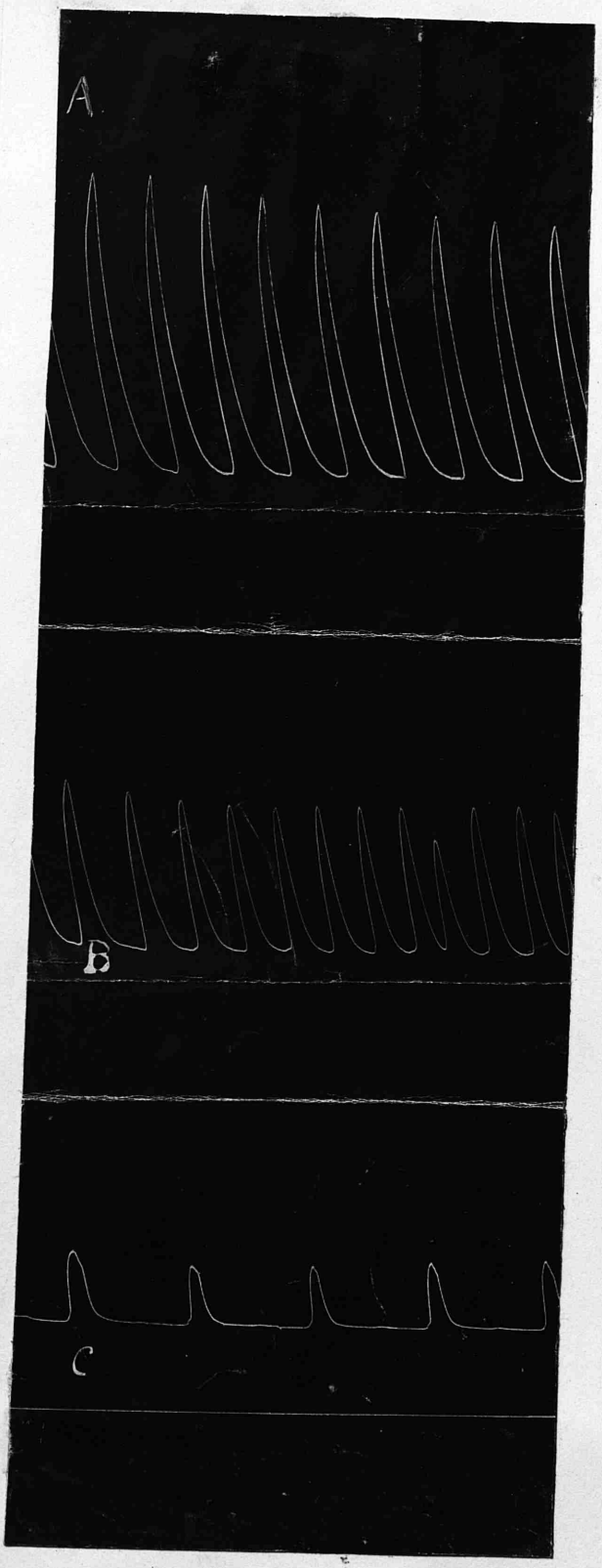


Fig. XVIII

FIGURE XIX.

Non-pregnant Uterus - Rat (118 grms).

Comparison between the contractions of

(A) the uterine end - 0.9" long,

(B) the ovarian end attached to the cervix and the ganglion - 0.7" long,

and (C) the ovarian end of the horn - 0.7" long,

(A) and (C) being unattached to the cervix and the ganglion.

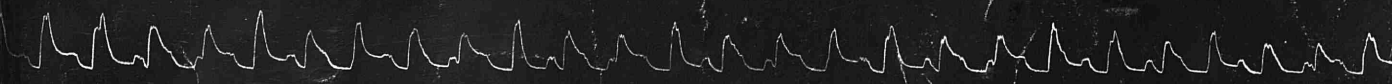
Fig XIX

A. Uterine end of horn (non-ganglionated) — 0·9".

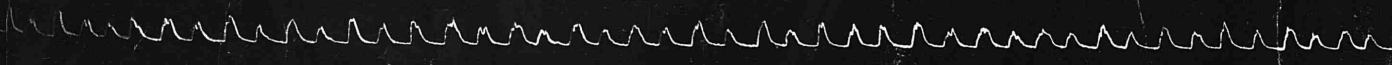
B. Ovarian end attached to cervix and ganglion — 0·7".

C. Ovarian end of horn (non-ganglionated) — 0·7".

A.



B.



C.

FIGURE XX.

Non-pregnant Uterus - Rat (210 grms).

Comparison between the contractions of (H) the non-ganglionated - 1" long - and (G) the ganglionated horn - 1" long - before -AO and after -OB removal of the cervical ganglion. (At O when the portion carrying the ganglion was removed from the portion (G) to equalise the trauma the lower free end of portion (H) was cut away.

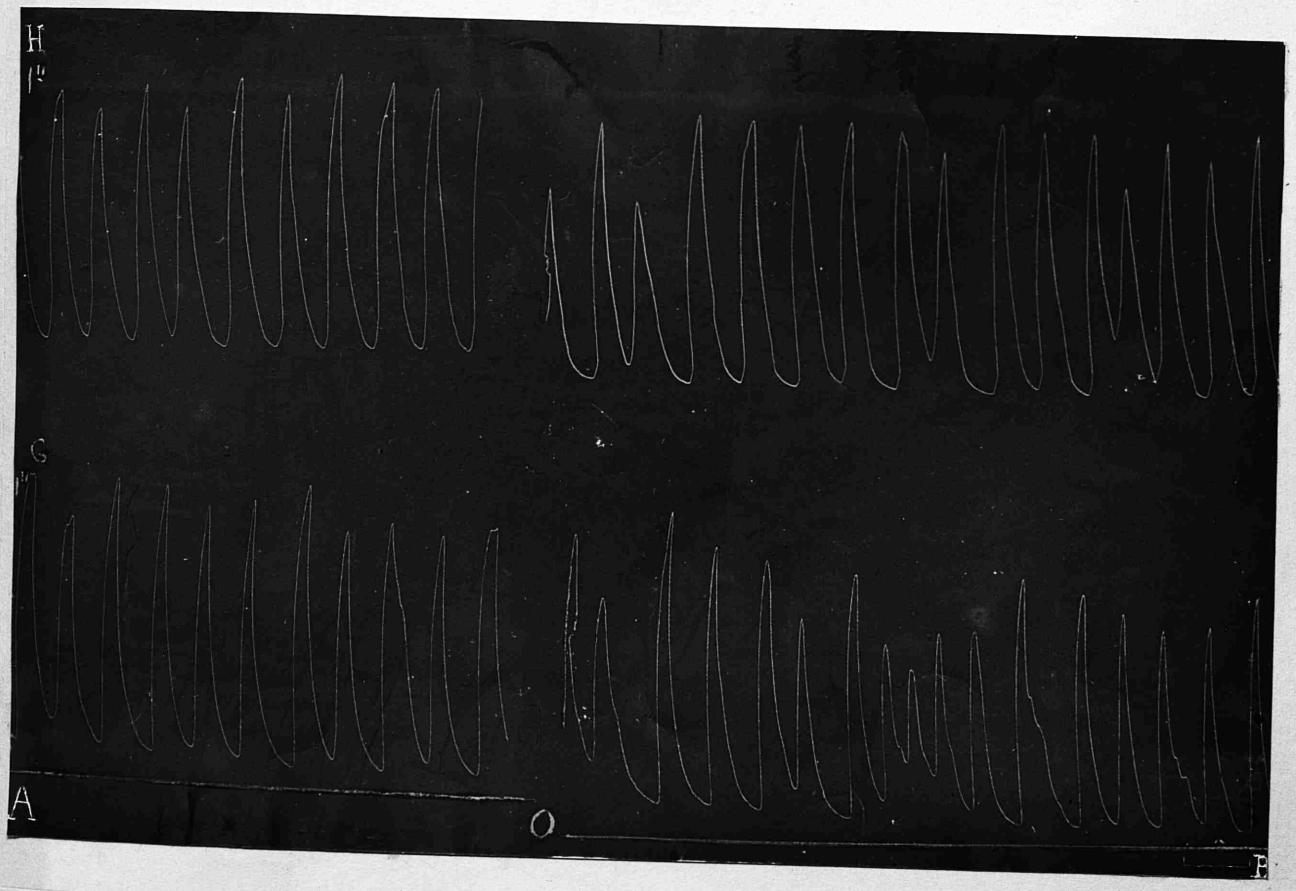


Fig. XX

FIGURE XXI.

Non-pregnant Uterus - Rat (200 grms).

Comparison between the contractions of (H) the non-ganglionated - 1" long - and (G) the ganglionated horn - 1" long - before -AO and after -OB removal of the cervical ganglion. (At O when the portion carrying the ganglion was removed from the strip (G) to equalise the trauma the lower free end of the strip (H) was cut away.

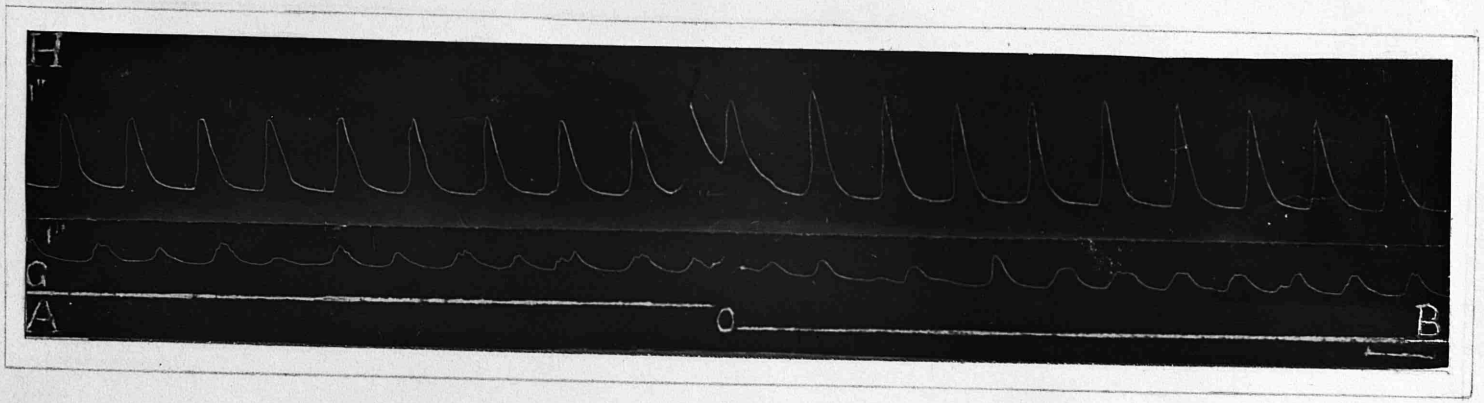


Fig. XXI

FIGURE XXII.

Non-pregnant Uterus - Rat (110 grms).

Comparison between the effects of Barium chloride on

(A) the ganglionated - 1.9" long, and

(B) the non-ganglionated horn - 2.1" long.

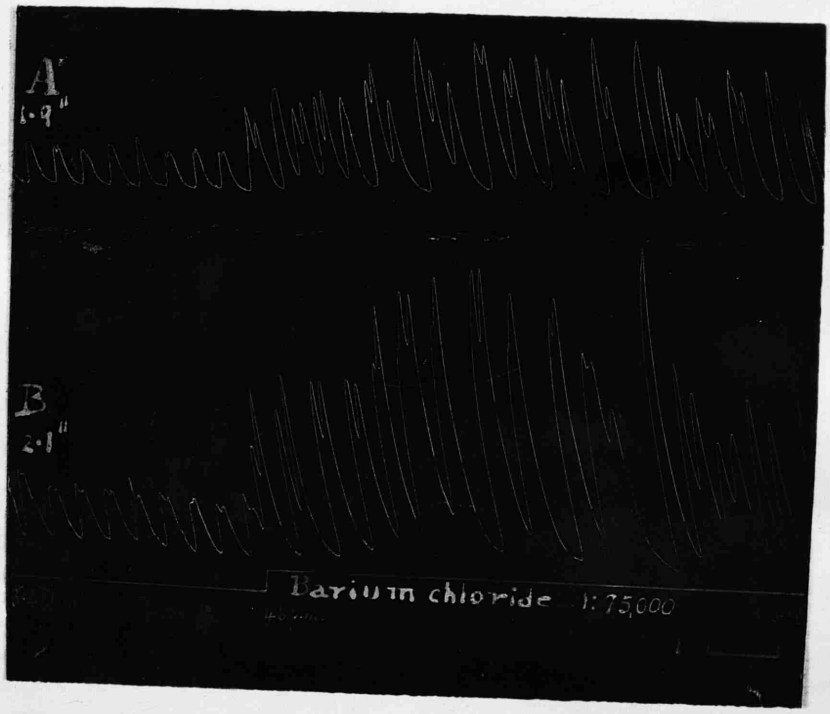


Fig. XXII

FIGURE XXIII.

Non-pregnant Uterus - Guineapig (525 grms).

The effect of Adrenalin 1:200,000 after Barium chloride 1:2,500 upon the non-ganglionated horn.

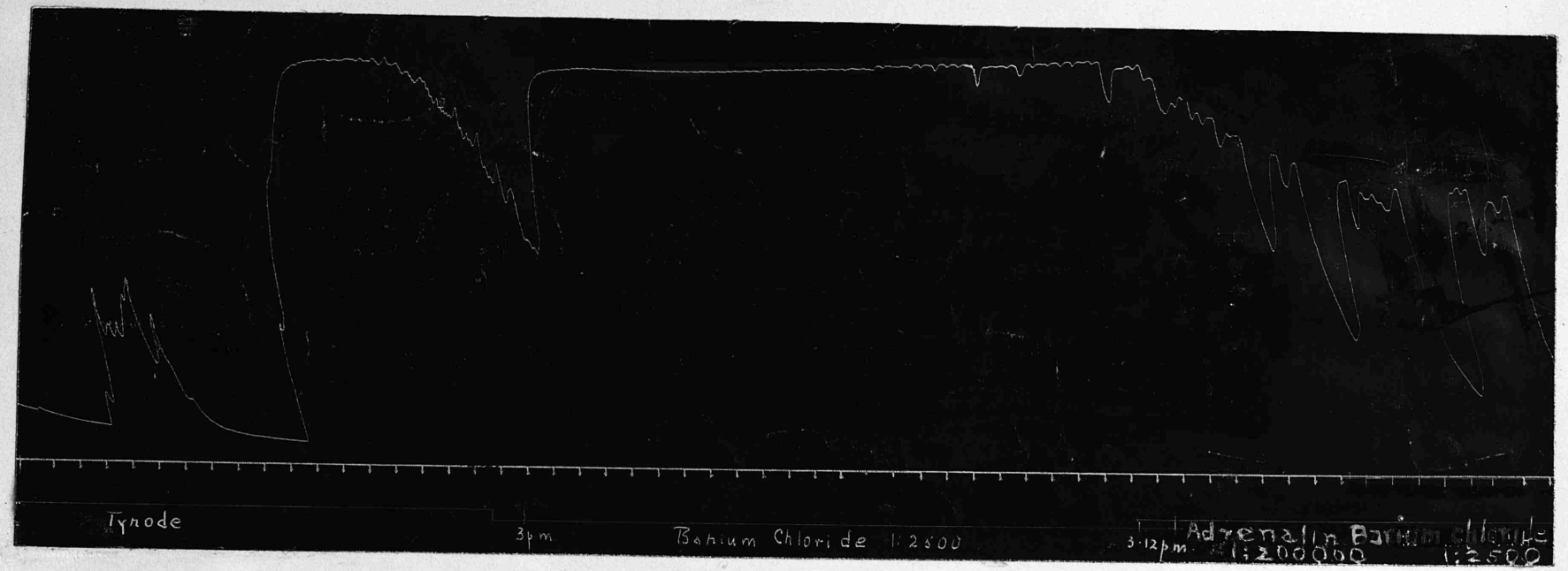

Tyrode
3 p m
Barium Chloride 1:2500
3-12 p m.
Adrenalin Barium chloride
1:200000
1:2500

Fig. XXIII

FIGURE XXIV.

Non-pregnant Uterus - Rat (195 grms).

Comparison between the effect of Adrenalin 1:166,700 upon a portion

(A) comprising the uterine end of the horn and the cervix carrying the ganglion.

(B) comprising the ovarian end of the horn unattached to the ganglion.

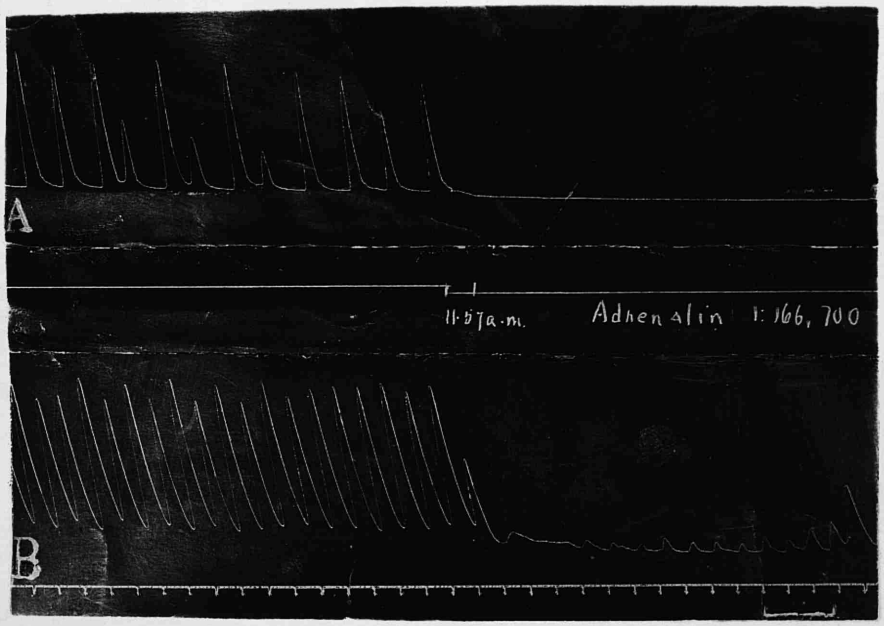


Fig. XXIV

FIGURE XXV.

Non-pregnant Uterus - Rat (160 grms).

The effect of Adrenalin 1:40,000,000 upon the ganglionated horn - 1.6" long.

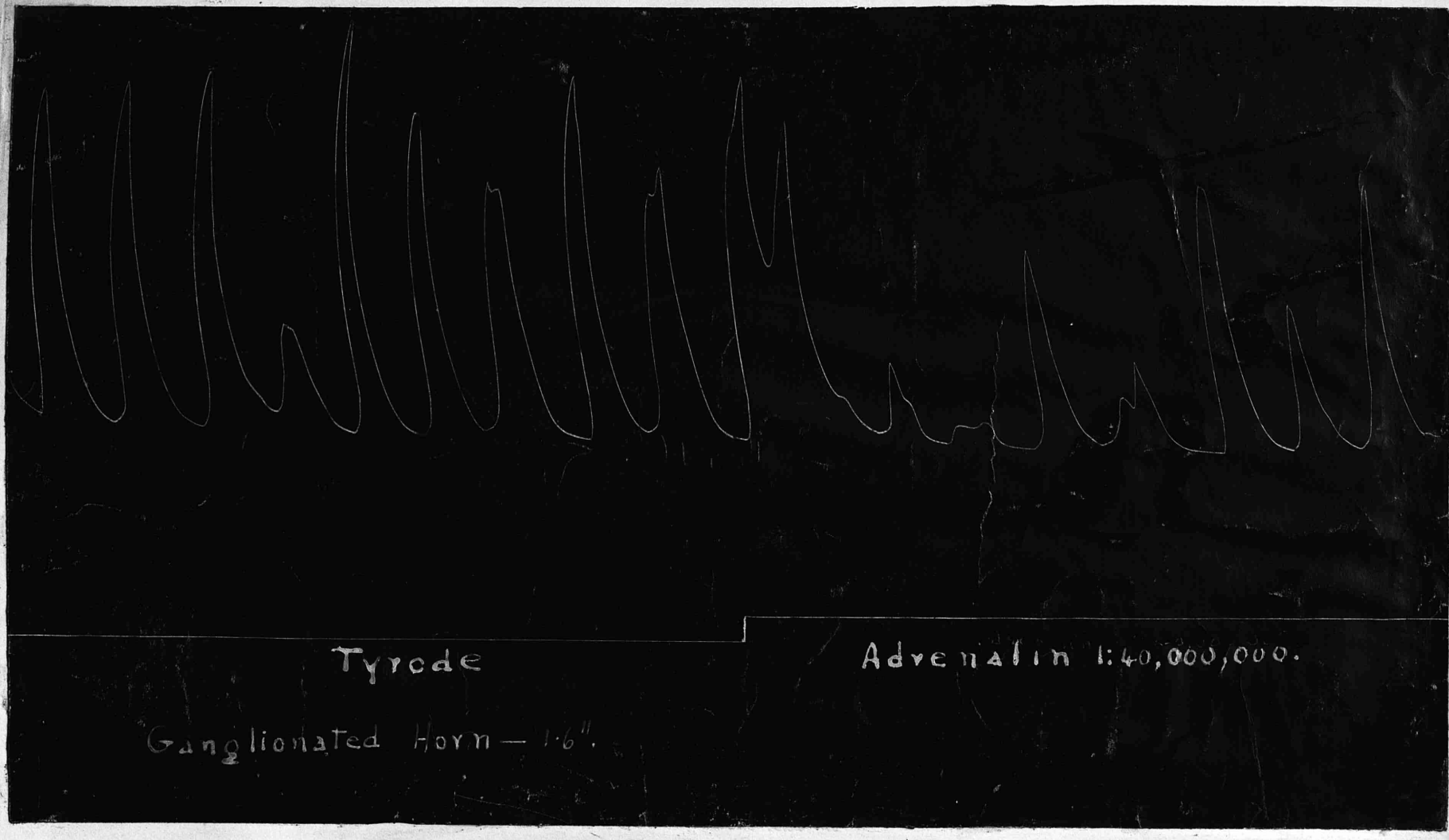


Fig. XXV

FIGURE XXVI.

Non-pregnant Uterus - Rat (180 grms).

Comparison between the effect of Pilocarpin nitrate 1:2,500 on

(A) the non-ganglionated horn - 0.5" long, and (B) the ganglionated horn - 0.8" long, each portion being from the ovarian end of the horns.

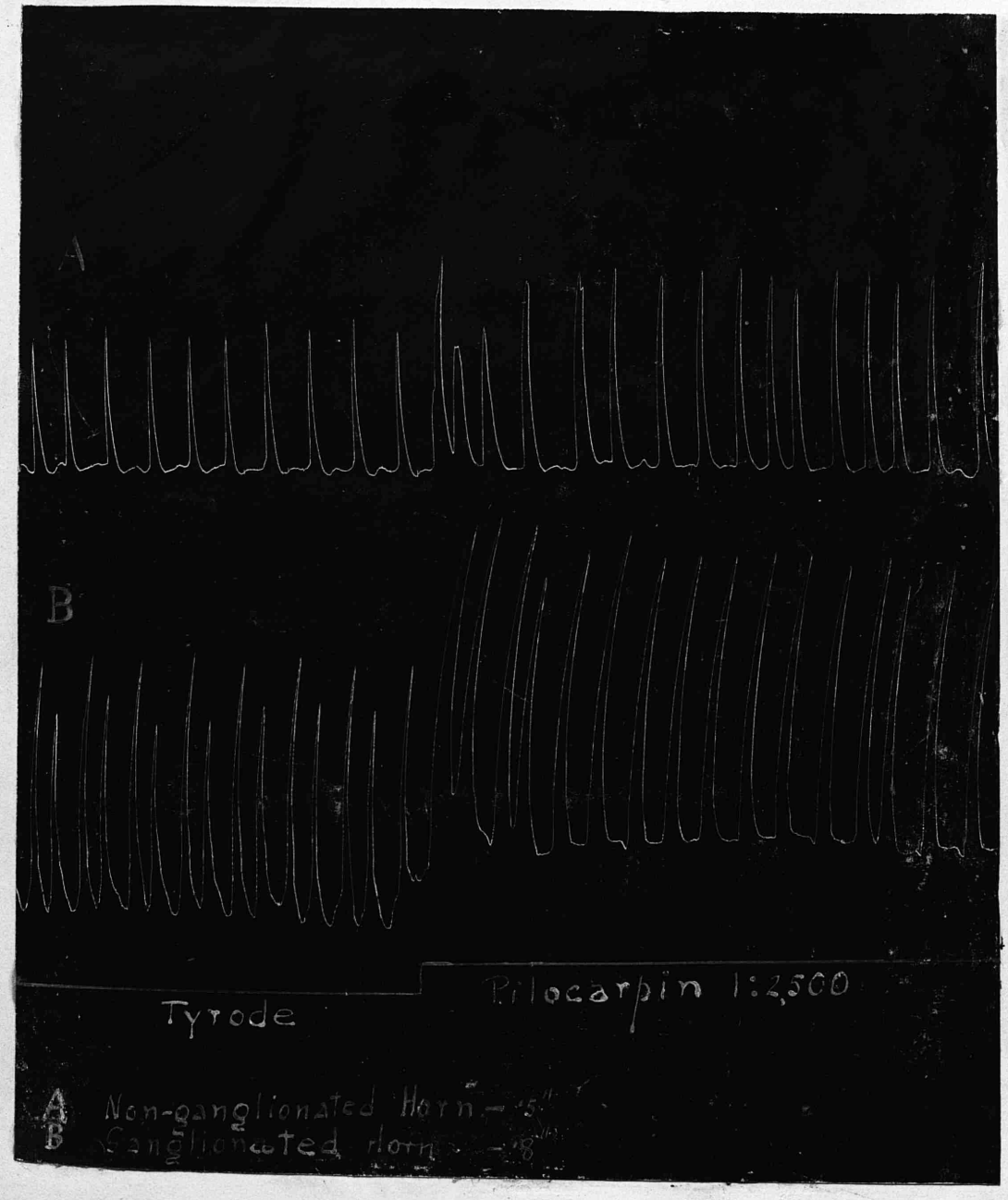

A
B
Tyrode
Pilocarpin 1:2,500
A Non-ganglionated Horn
B Ganglionated Horn

Fig XXVI

FIGURE XXVII.

Pregnant Uterus - Rat (190 grms).

Comparison between the effect of Pilocarpin 1:2,500 on

(A) the ganglionated - $1^{3}/8$" long, and

(B) the non-ganglionated horn - $1\frac{3}{4}$" long.

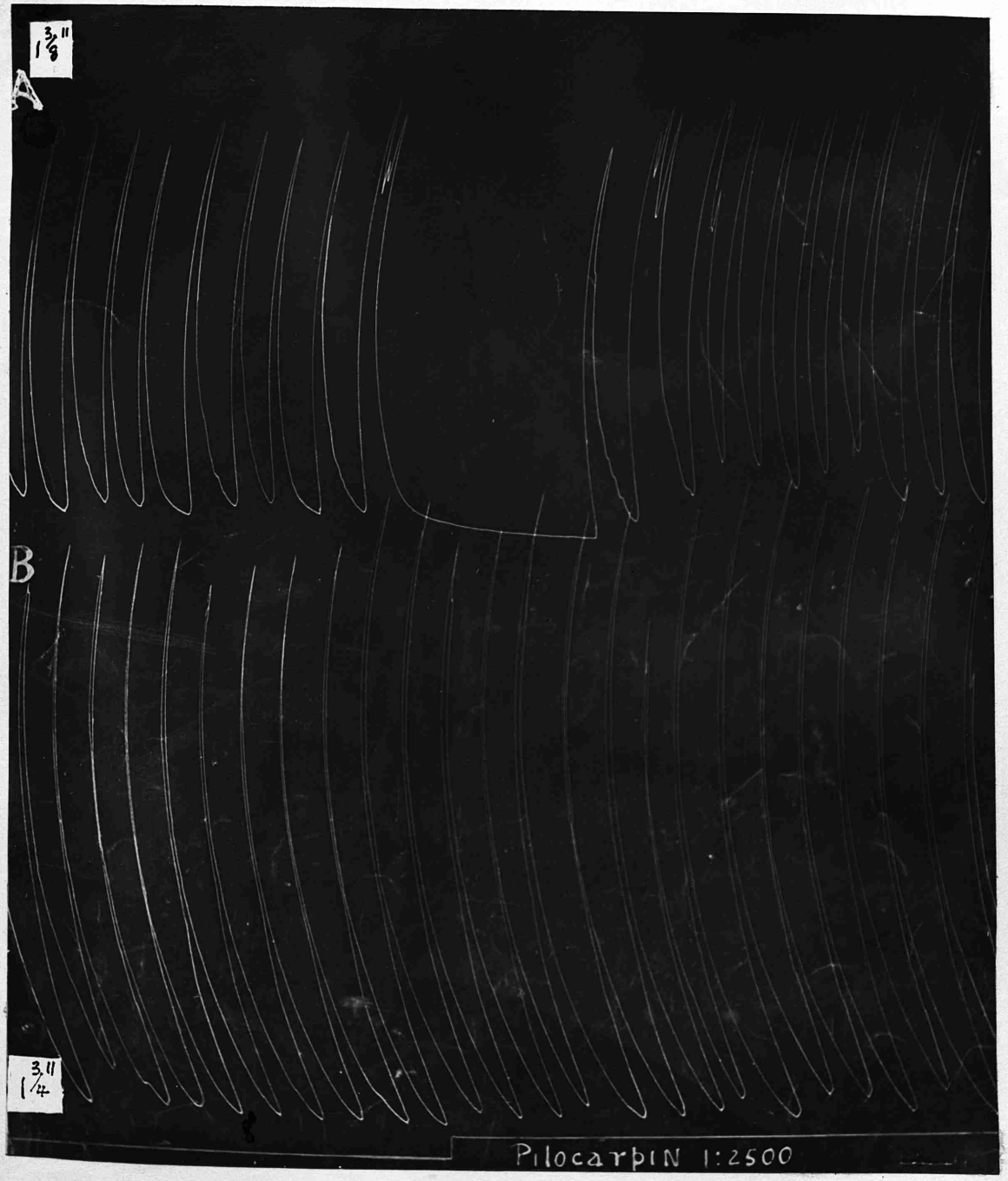


Fig. XXVII

FIGURE XXVIII.

Pregnant Uterus - Rat (220 grms).

Comparison between the effect of Pilocarpin 1:2,000 upon a portion

(A) comprising the uterine end of the horn and the cervix carrying with it the ganglion, and upon a portion

(B) from the ovarian end of the horn.

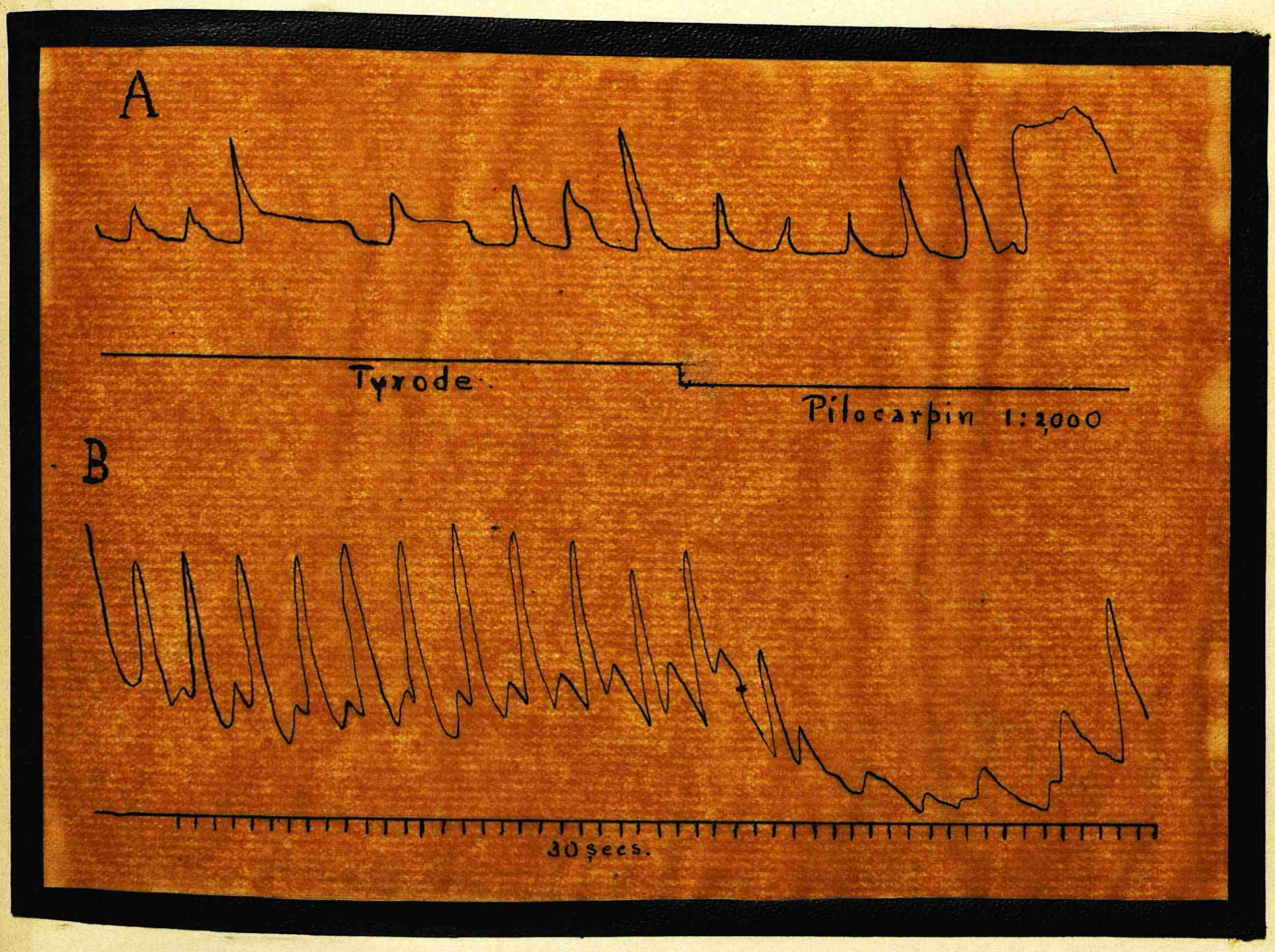


Fig XXVIII

FIGURE XXIX.

Non-pregnant Uterus - Rat (170 grms).

Comparison between the effect of Eserin sulphate 1:1,550 on

(A) the whole horn attached to the cervix and the ganglion - 1.2" long,

(B) the ovarian end - 0.75" long, and

(C) the uterine end - 0.3" long.

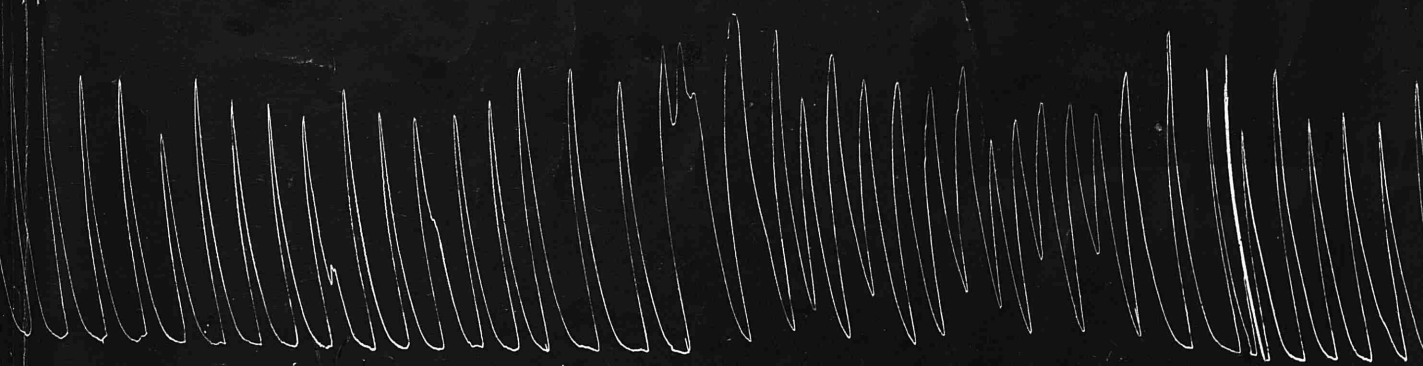
Fig XXIX

A. Whole horn attached to cervix and ganglion. — 1·2".

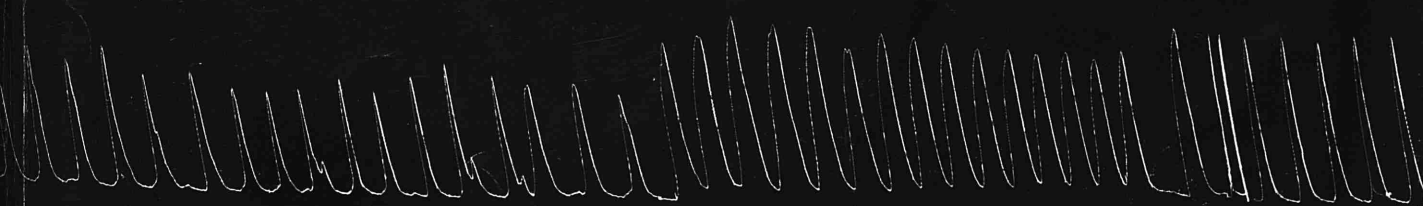
B Ovarian end of horn (non-ganglionated). — 0·75"

C Uterine end of horn (non-ganglionated). — 0·3".

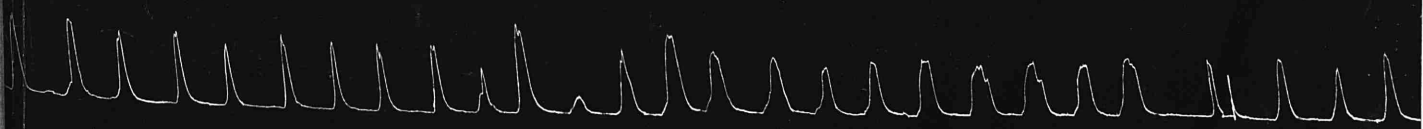
A



B



C.



Tyrode

Physostigmin 1:1550
Eserin Sulphate.

FIGURE XXX.

Non-pregnant Uterus - Rat (225 grms).

The effect of Atropin 1:500 after Physostigmin 1:1,550 and secondly after Physostigmin 1:775 upon the non-ganglionated horn - 1.1" long.

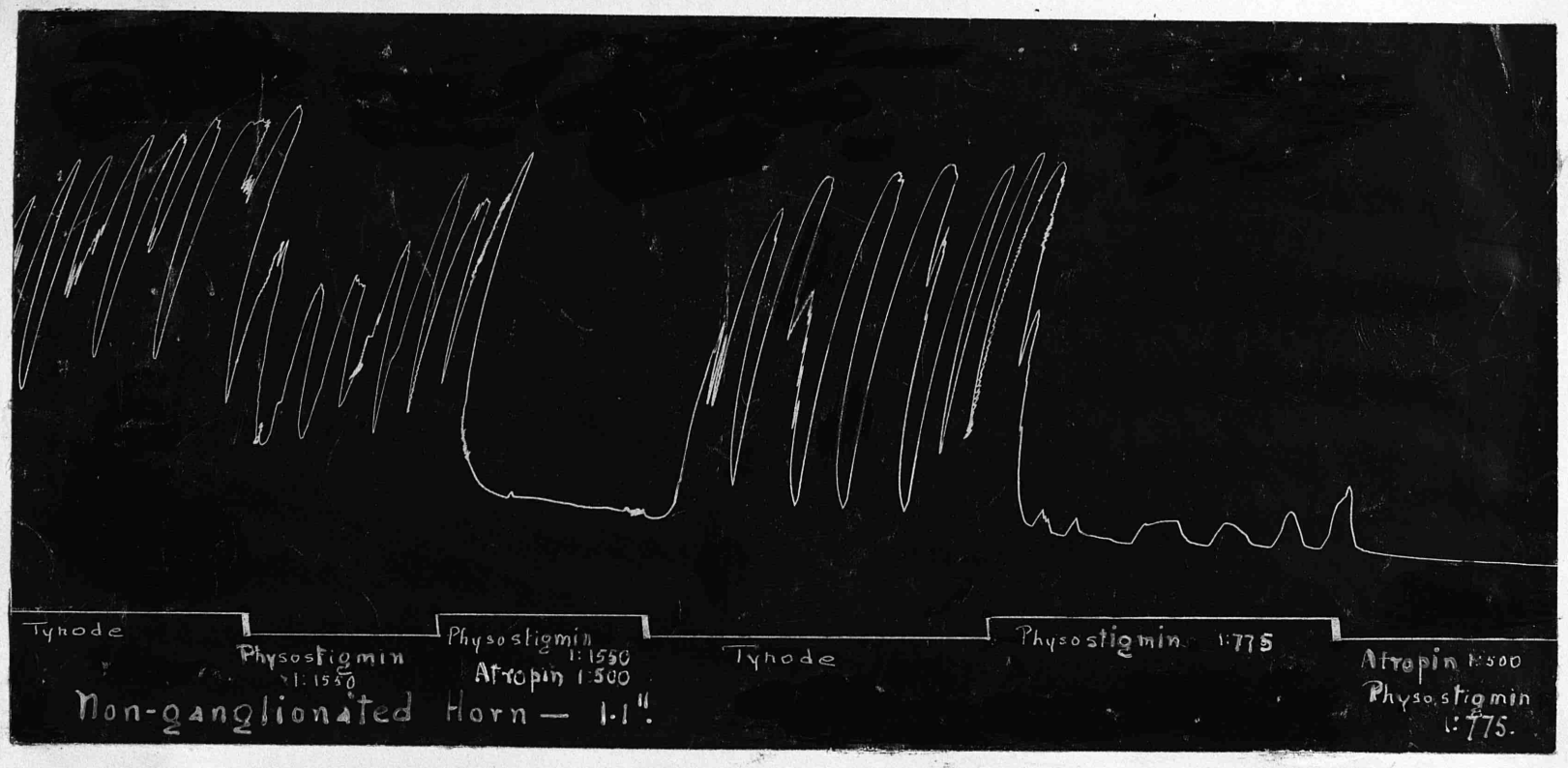

Tyrode
Physostigmin 1:1550
Physostigmin 1:1550
Atropin 1:500
Tyrode
Physostigmin 1:775
Atropin 1:500
Physostigmin 1:775.
Non-ganglionated Horn — 1·1".

Fig. XXX

FIGURE XXXI.

Non-pregnant Uterus - Rat (230 grms).

Comparison between the effect of Atropin 1:1,000 on

(A) the non-ganglionated horn - $1\frac{3}{8}$" long and

(B) the ganglionated horn - $1\frac{1}{4}$" long.


A.
B.
Tyrode
Atropin 1:1000
2.47 p.m.
3.16 p.m.
A. Non-ganglionated 1 3/8" ; B. Ganglionated Horn - 1 1/4"

Fig XXXI

FIGURE XXXII.

Non-pregnant Uterus - Guineapig (400 grms).

Comparison between the effect of Atropin 1:1,000 followed by Adrenalin 1:250,000 on

(A) the horn unattached, and

(B) the uterine end of the horn and cervix attached to the ganglion.

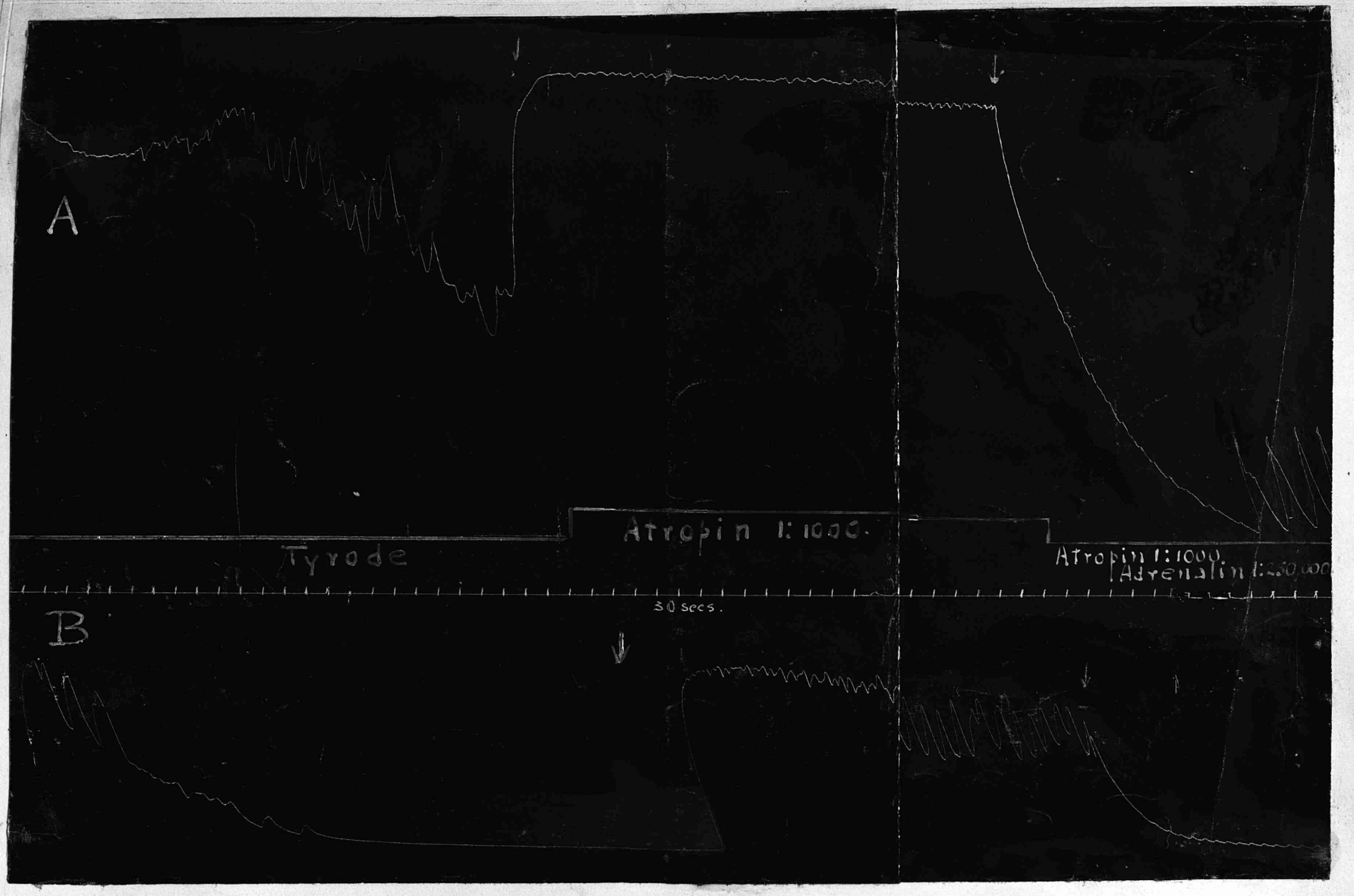


Fig XXXII

FIGURE XXXIII.

Non-pregnant Uterus - Rat (190 grms).

Comparison between the effect of Nicotin 1:2,000 on two non-ganglionated portions of horn:-

(A) $1\frac{3}{4}$" , and

(B) $2\frac{1}{4}$" long.

Fig XXXIII

Tyrode

Nicotin 1:2,000

1 3/4" } non-ganglionated horns.

FIGURE XXXIV.

Non-pregnant Uterus - Rat (180 grms).

Comparison between the effect of Nicotin 1:1,000 upon

(A) the ganglionated horn - $2\frac{3}{4}$" long, and

(B) the non-ganglionated horn - $2^3/8$" long.

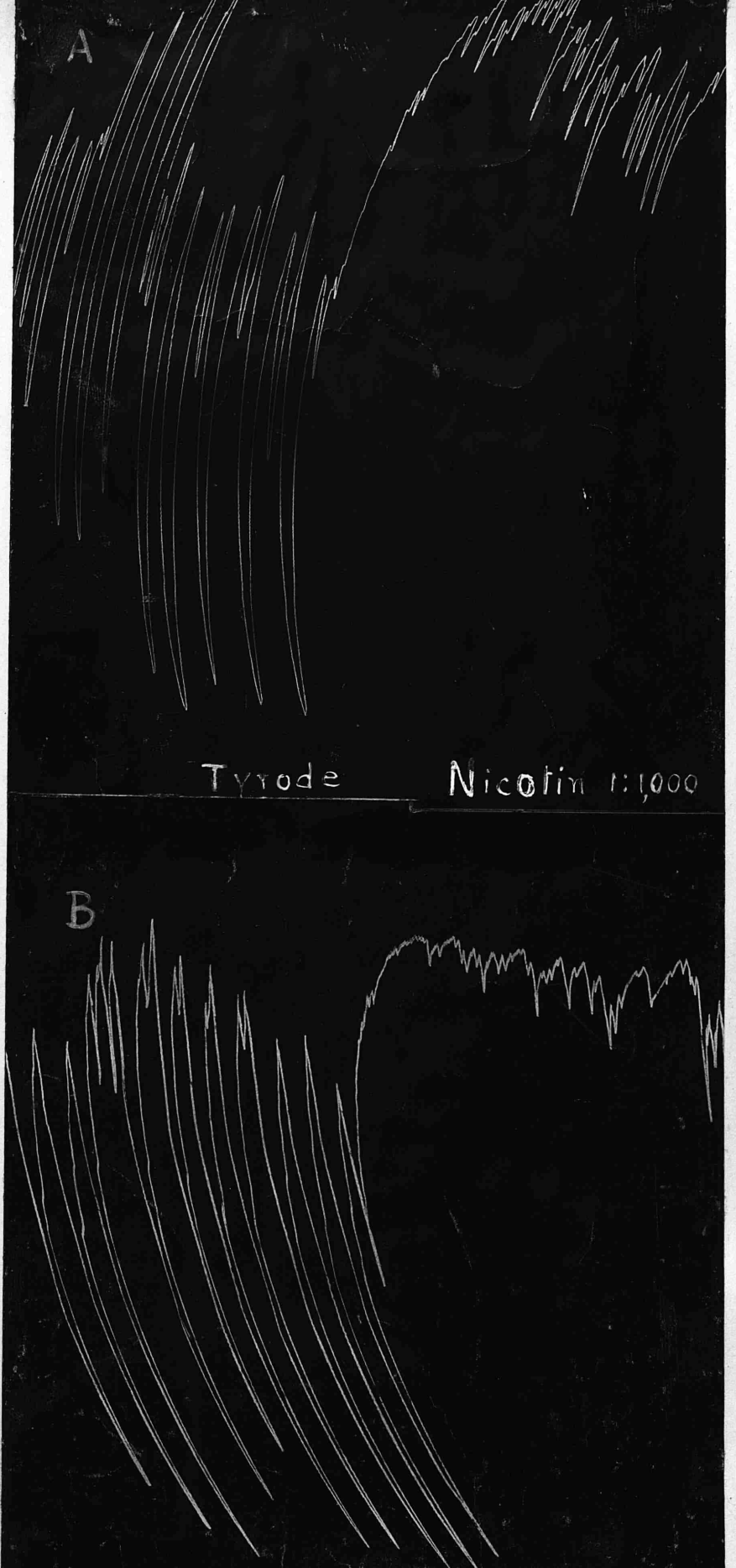


Fig
XXXIV

FIGURE XXXV.

Non-pregnant Uterus - Guineapig (380 grms).

Augmentory effect produced by Nicotin 1:2,500 on the non-ganglionated horn.

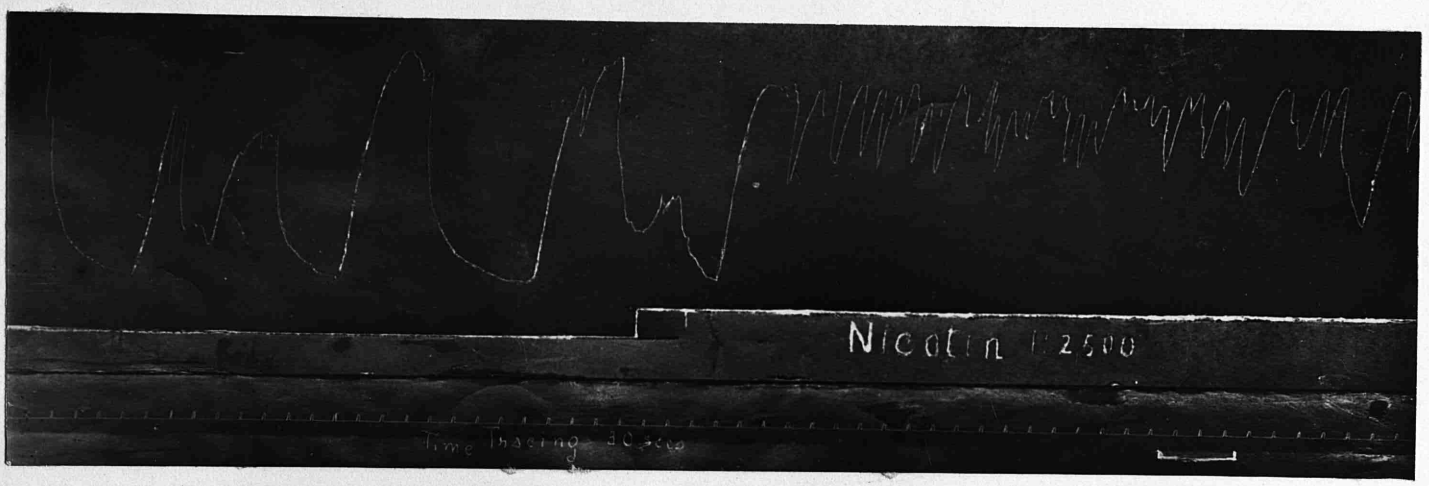


Fig. XXXV

FIGURE XXXVI.

Non-pregnant Uterus - Rat (160 grms).

Comparison between the effect of Ergotoxin phosphate 1:10,000,000 upon

(A) the non-ganglionated - 2.2" long, and

(B) the ganglionated horn - 1.6" long.

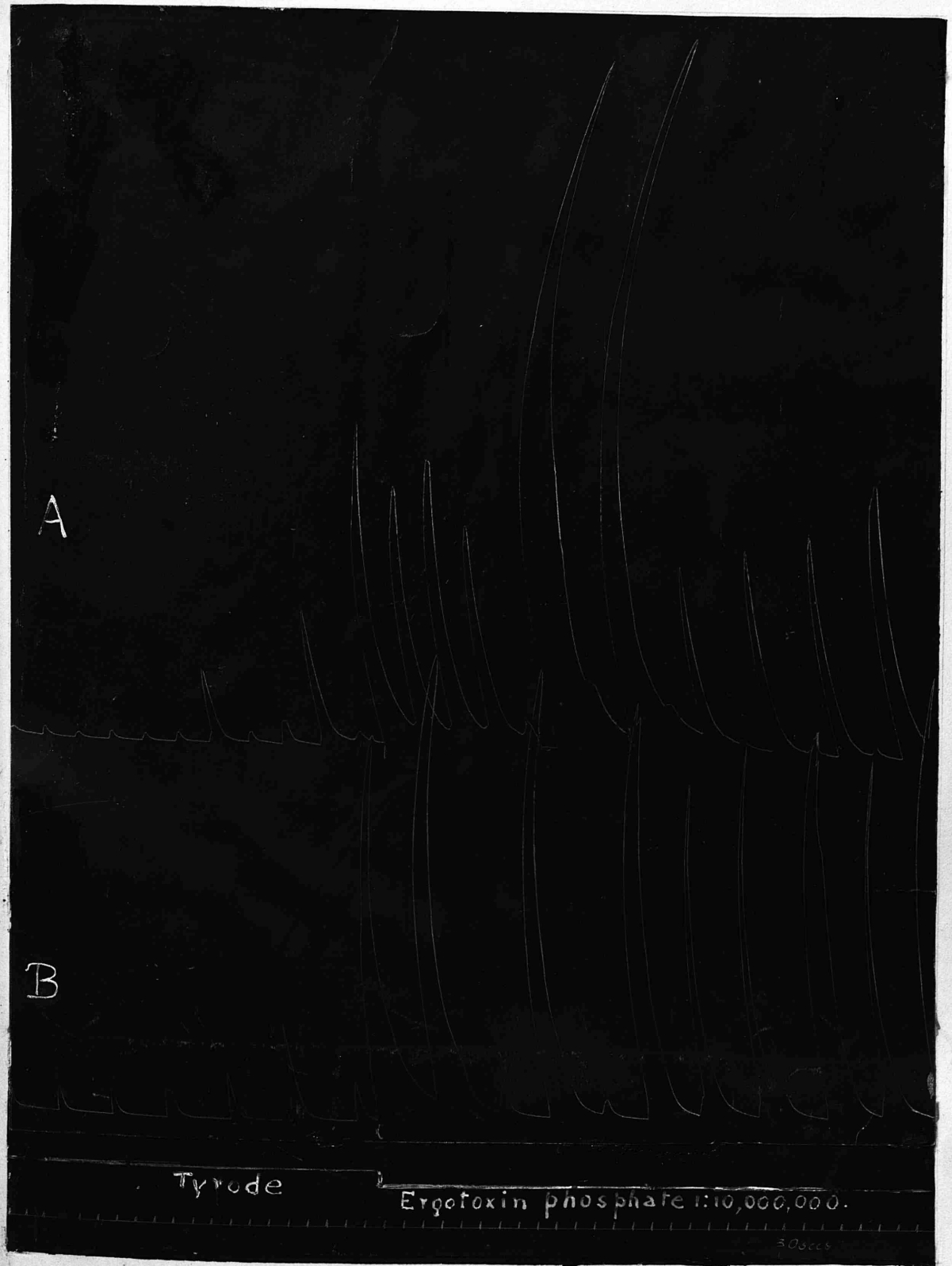


Fig XXXVI

FIGURE XXXVII.

Pregnant Uterus - Guineapig (590 grms).

Effect of Ergotamin tartrate 1:1,000 upon the ganglionated horn.

Fig. XXXVII

FIGURE XXXVIII.

Non-pregnant Uterus - Rat (135 grms).

Comparison between the effect of Physostigmin 1:3,000 followed by Atropin 1:500 upon

(A) the non-ganglionated - $1\frac{1}{4}$" long, and

(B) the ganglionated horn - $1\frac{1}{4}$" long.

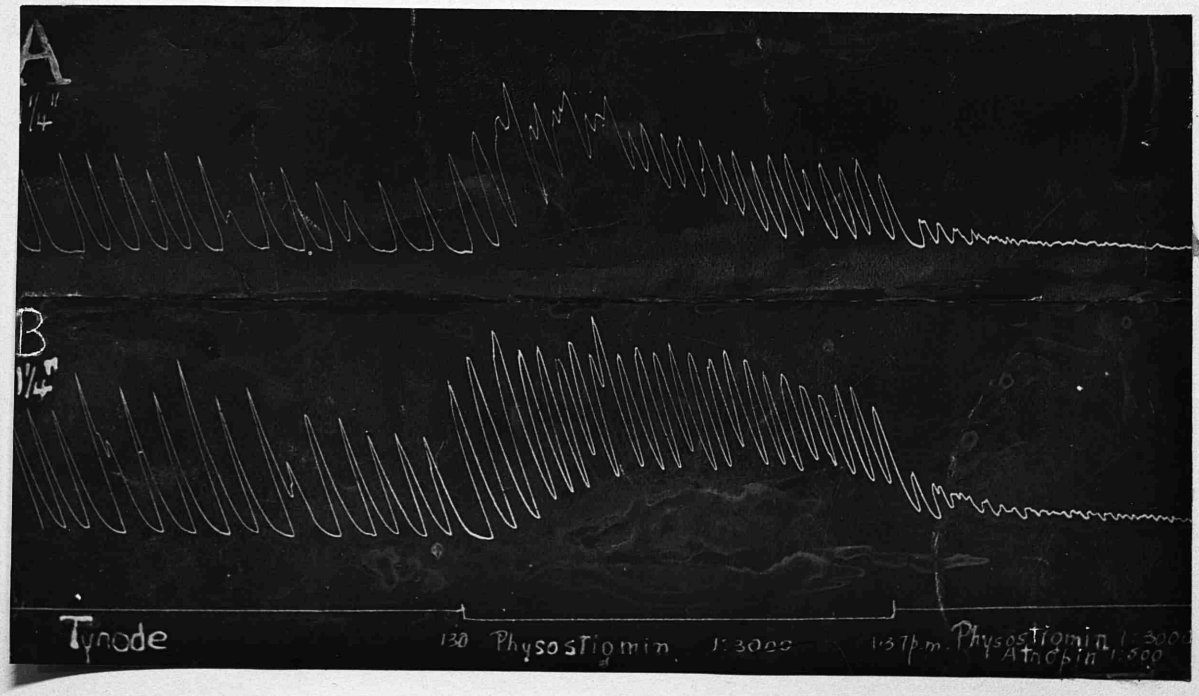

A
1/4"
B
1/4"
Tynode
130 Physostigmin 1:3000
1:37 p.m. Physostigmin 1:3000
Atropin 1:500

Fig XXXVIII

FIGURE XXXIX.

Non-pregnant Uterus - Rat (195 grms).

Effect of Barium chloride 1:1,250 after Adrenalin 1:166,700 upon a portion (0.75" long) comprising the uterine end of the horn and the cervix attached to the ganglion.

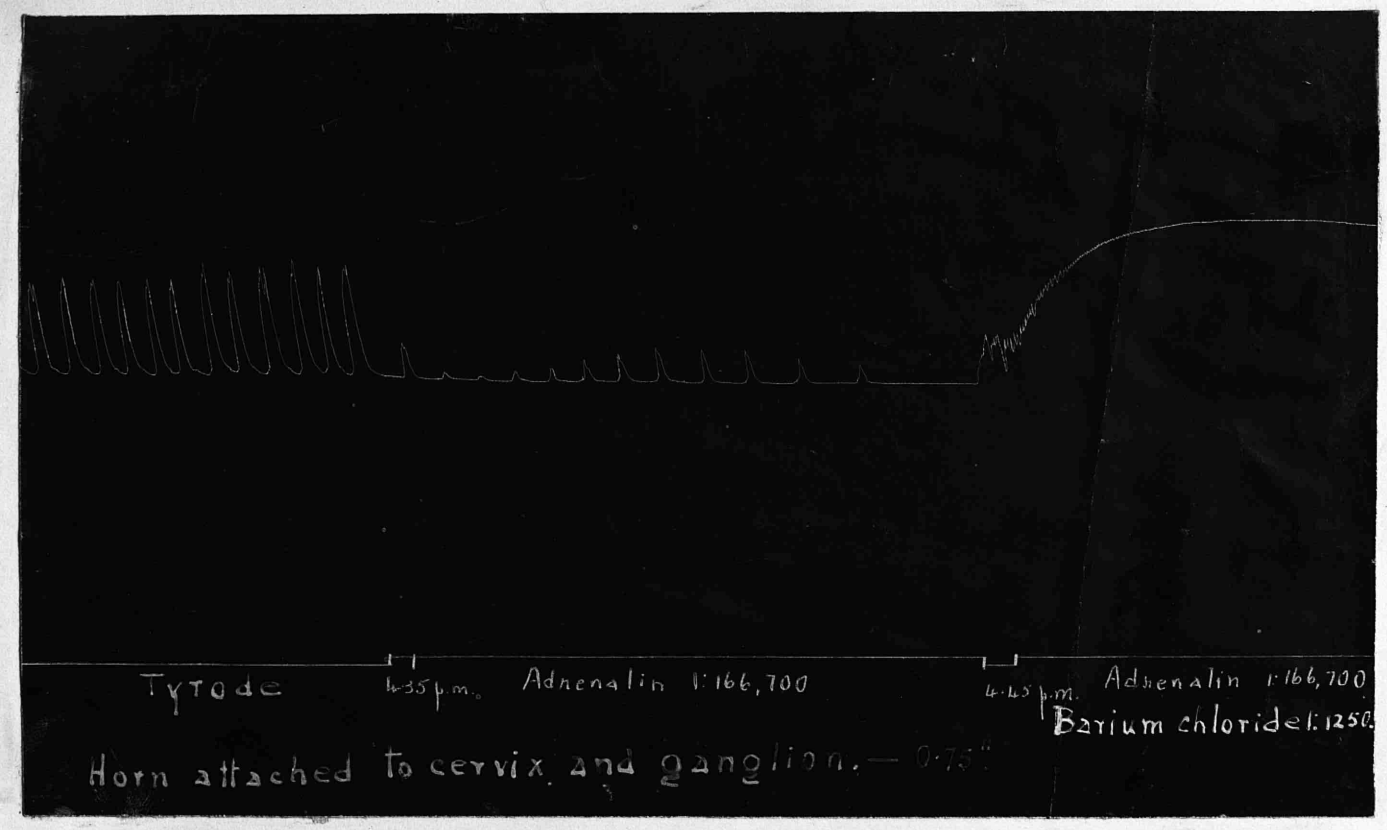

Tytode
4.35 p.m. Adrenalin 1:166,700
4.45 p.m. Adrenalin 1:166,700
Barium chloride 1:1250
Horn attached to cervix and ganglion. — 0·75"

Fig. XXXIX

FIGURE XL.

Non-pregnant Uterus - Rat (145 grms).

Effect of Atropin 1:1,000 after Barium Chloride 1:1,000 upon

(A) the ganglionated - $1\frac{1}{2}$" long, and

(B) the non-ganglionated horn - 1" long.

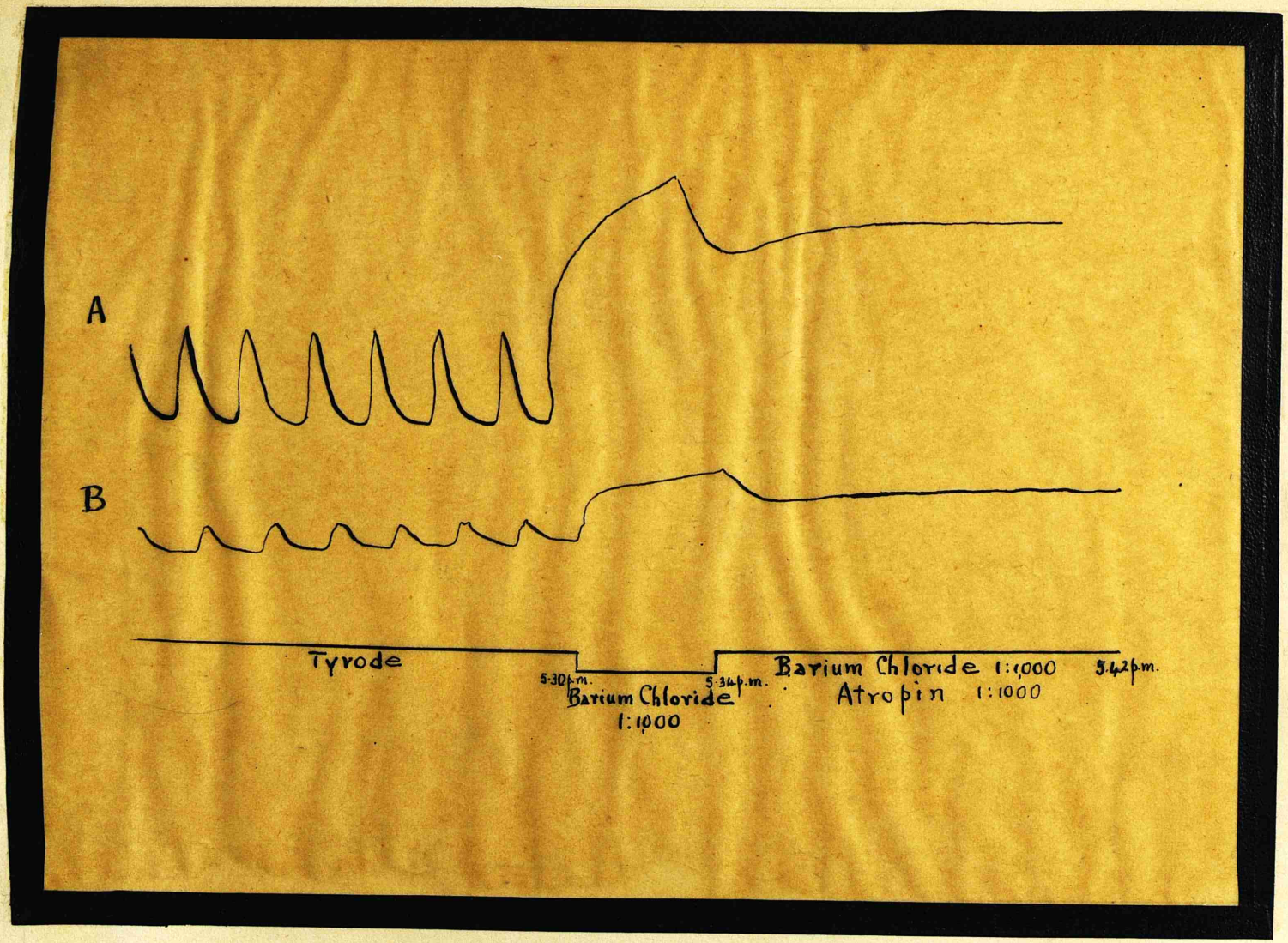

A
B
Tyrode
5:30 p.m.
Barium Chloride
1:1000
5:34 p.m.
Barium Chloride 1:1000
Atropin 1:1000
5.42 p.m.

Fig. XL

FIGURE XLI.

Non-pregnant Uterus - Rat (145 grms).

A. The effect of Nicotin 1:1,000 after Barium Chloride 1:2,500.

B. The effect of Barium Chloride 1:2,500 after Nicotin 1:1,000

upon the non-ganglionated horn - 1" long.

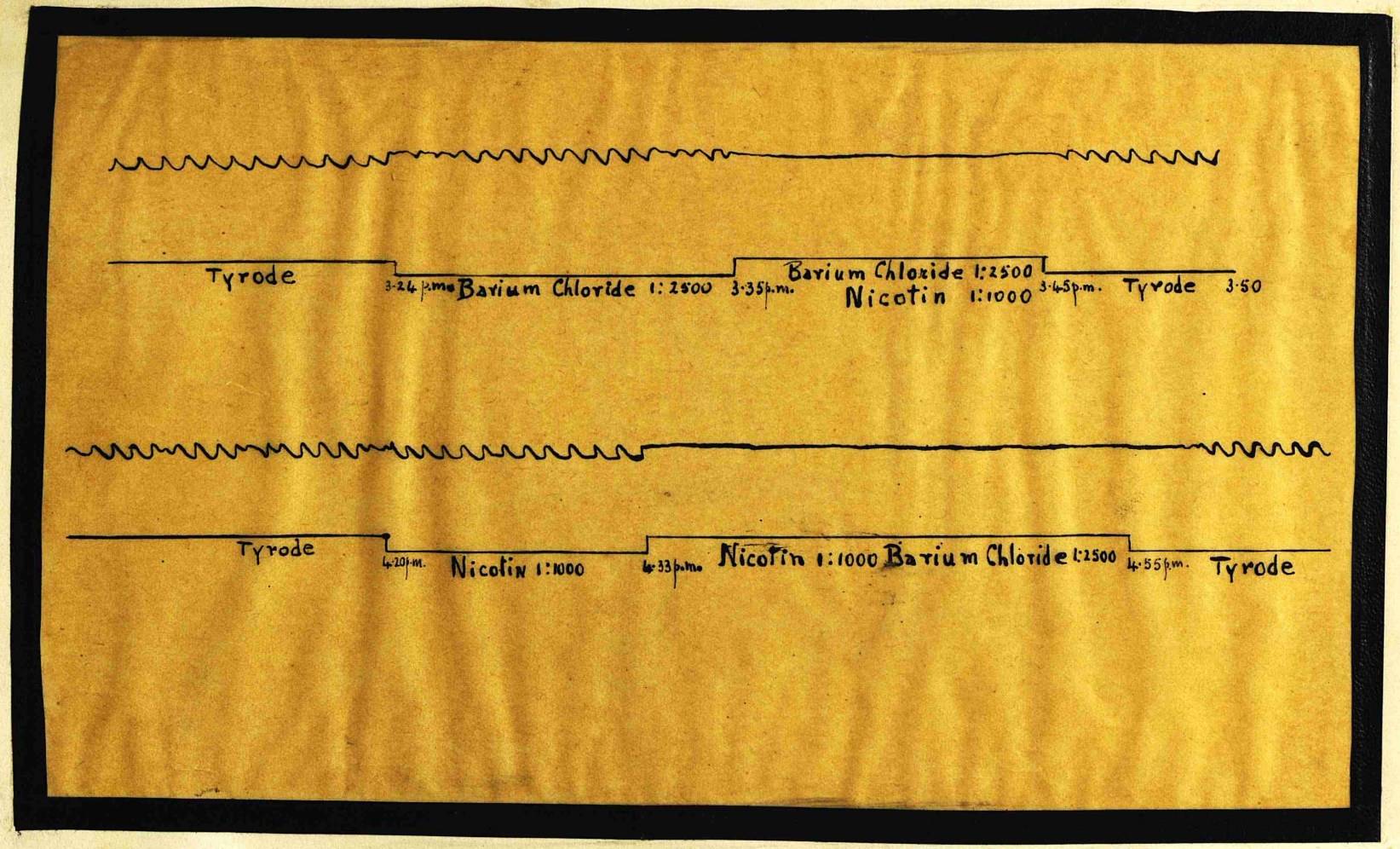

Tyrode
3-24 p.m.
Barium Chloride 1: 2500
3-35 p.m.
Barium Chloride 1:2500
Nicotin 1:1000
3-45 p.m.
Tyrode
3-50
Tyrode
4-20 p.m.
Nicotin 1:1000
4-33 p.m.
Nicotin 1:1000
Barium Chloride 1:2500
4-55 p.m.
Tyrode

Fig. XLI.

FIGURE XLII.

Non-pregnant Uterus - Rat (210 grms).

Effect of Pilocarpin 1:2,000 followed by Adrenalin 1:100,000 (injected into the bath) upon the non-ganglionated horn - 1" long.

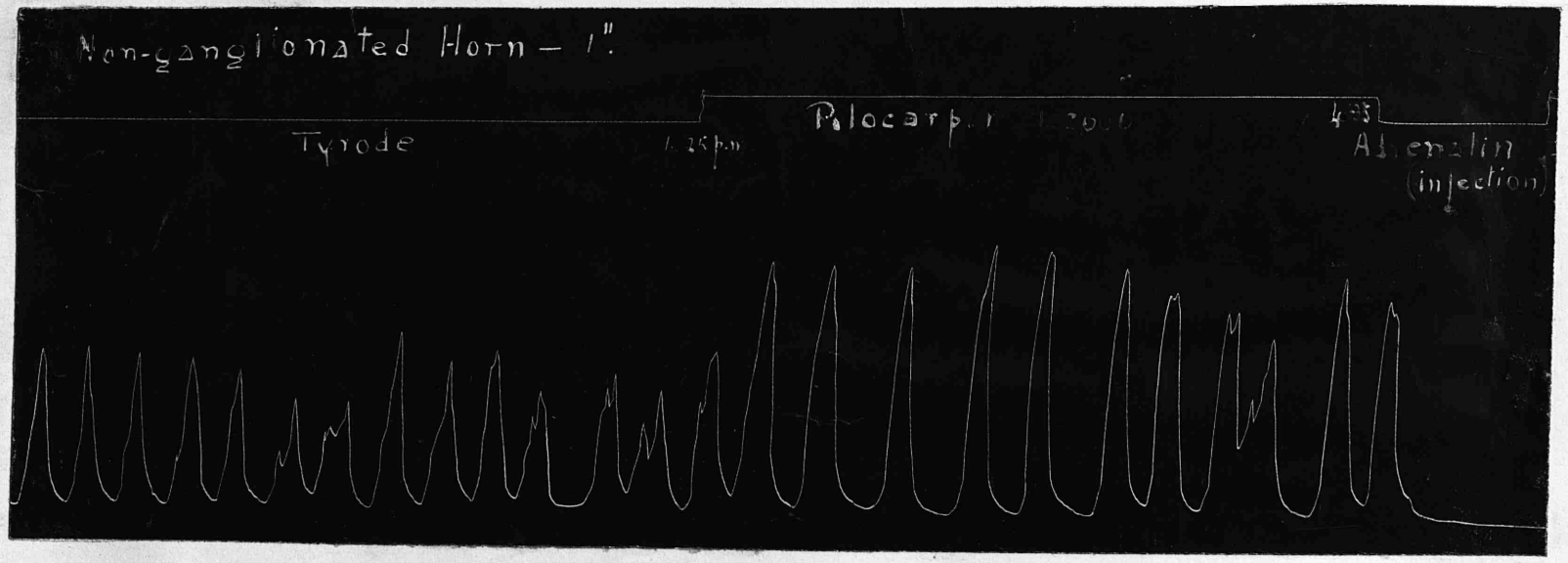

Non-ganglionated Horn – 1".
Tyrode
Pilocarpine
Adrenalin
(injection)

Fig. XLII

FIGURE XLIII.

Non-pregnant Uterus - Rat. (160 grms).

Effect of Adrenalin 1:100,000 after Physostigmin 1:2,500 on the non-ganglionated horn.

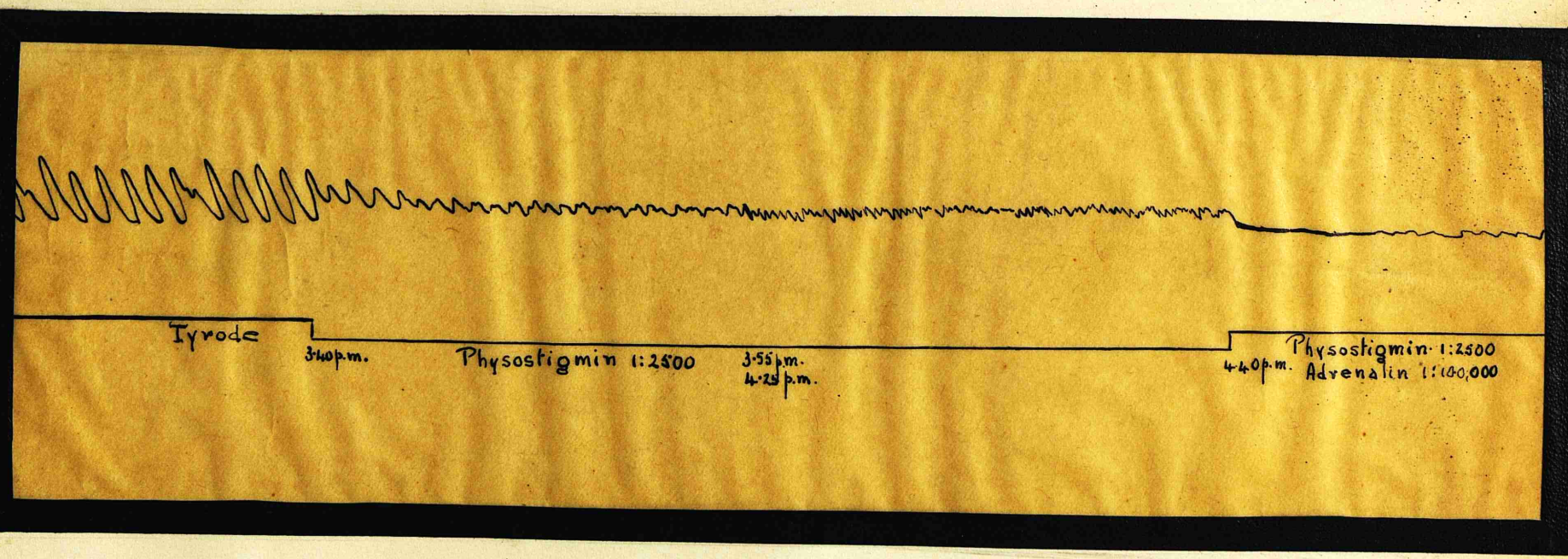

Tyrode
3.40 p.m.
Physostigmin 1:2500
3.55 p.m.
4.25 p.m.
Physostigmin 1:2500
4.40 p.m. Adrenalin 1:100,000

Fig. XLIII

FIGURE XLIV.

Pregnant Uterus - Guineapig (590 grms).

Effect of Physostigmin 1:4,600 upon a strip treated with Adrenalin 1:100,000.

Fig XLIV.

FIGURE XLV.

Non-pregnant Uterus - Rat. (145 grms).

Effect of Adrenalin 1:166,700 after Atropin 1:670 on the non-ganglionated horn.

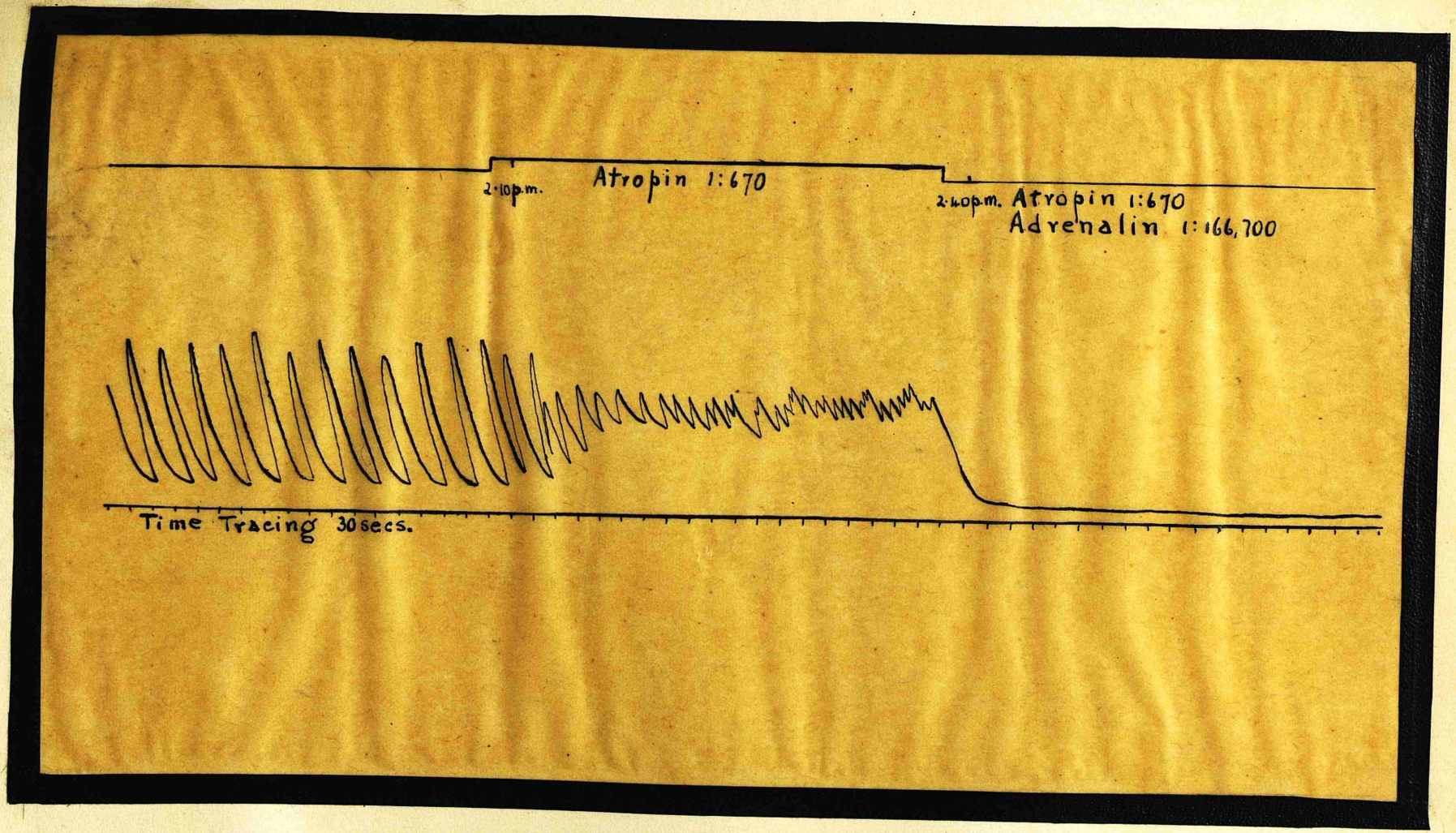

2·10p.m.
Atropin 1:670
2·40p.m. Atropin 1:670
Adrenalin 1:166,700
Time Tracing 30secs.

Fig. XLV

FIGURE XLVI.

Non-pregnant Uterus - Rat (145 grms).

Comparison between the effect of Nicotin 1:1000 followed by Adrenalin 1:400,000 upon

(A) the non-ganglionated - $1\frac{1}{4}$" long, and

(B) the ganglionated horn - $1\frac{1}{4}$" long.

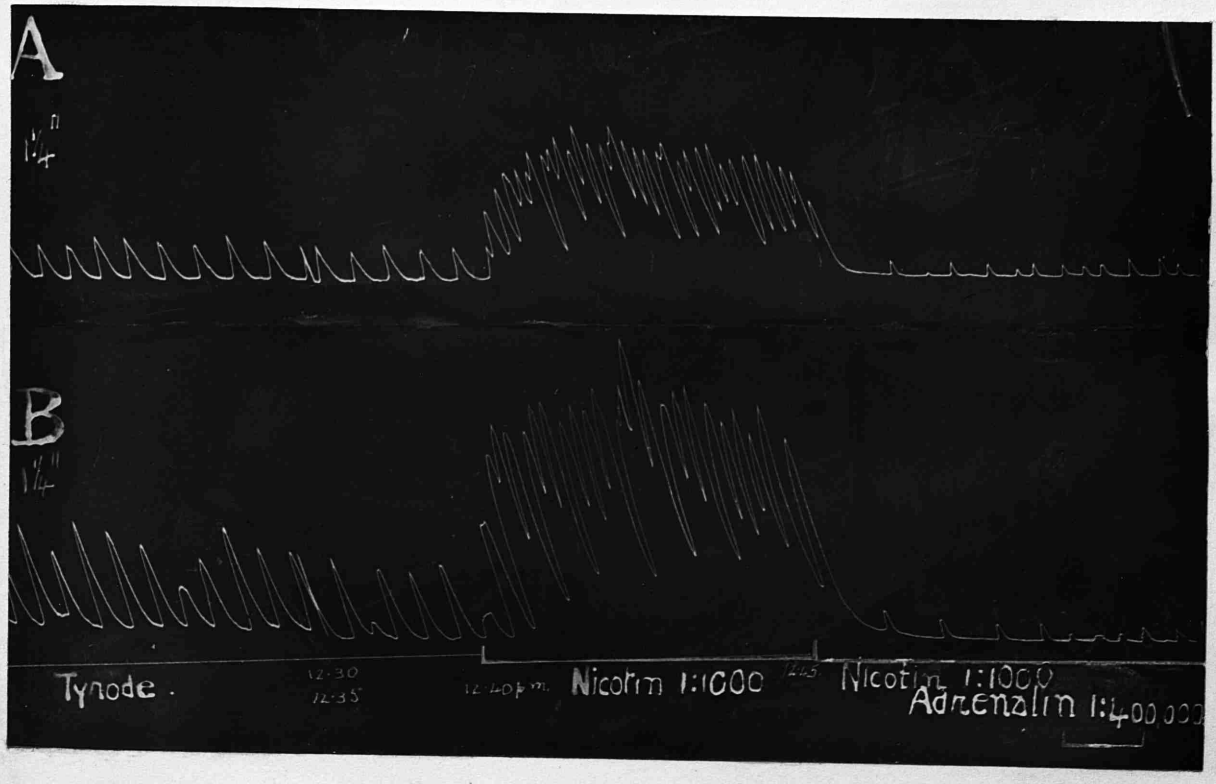

A
B
Tynode.
12·30
12·35
12·40 p.m.
Nicotin 1:1000
Nicotin 1:1000
Adrenalin 1:400,000

Fig. XLVI

FIGURE XLVII.

Pregnant Uterus - Rat (220 grms).

Effect of Ergotamin tartrate 1:1000 after Adrenalin 1:166,700 upon a portion comprising the uterine end of the horn and cervix carrying with it the ganglion.

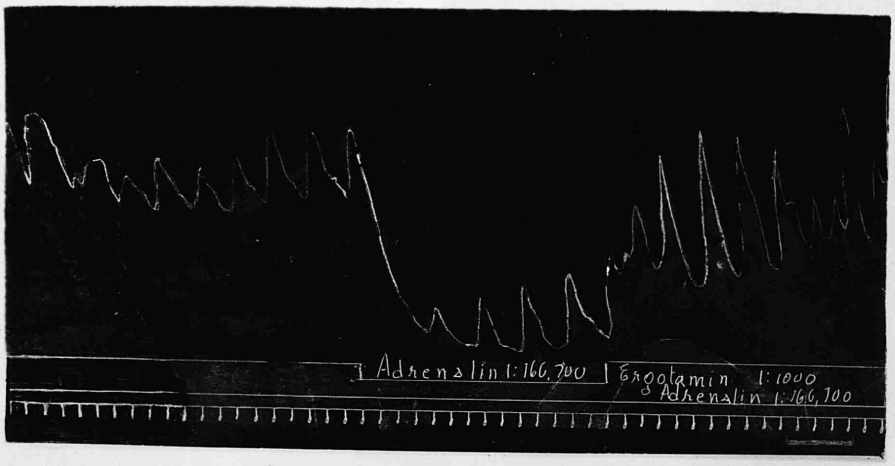


Fig XLVII

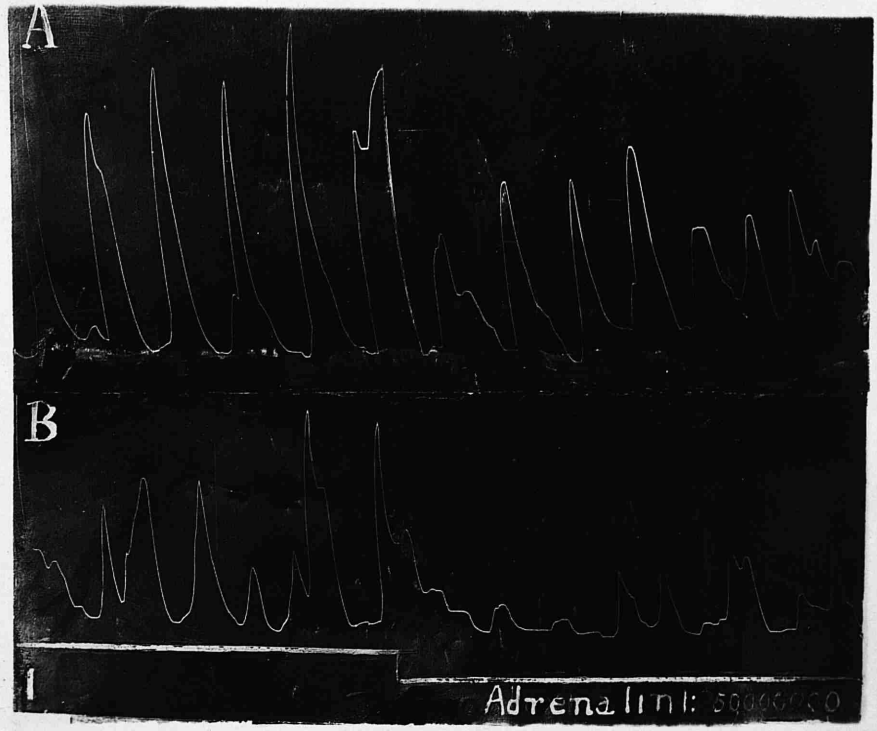
FIGURE XLVIII.

Non-pregnant Uterus - Rat (160 grms).

Comparison between the effect of Adrenalin 1:50,000,000 (i) before and (ii) after treatment of

(A) the ganglionated and

(B) the non-ganglionated horn with Ergotoxin phosphate 1:2,500,000.



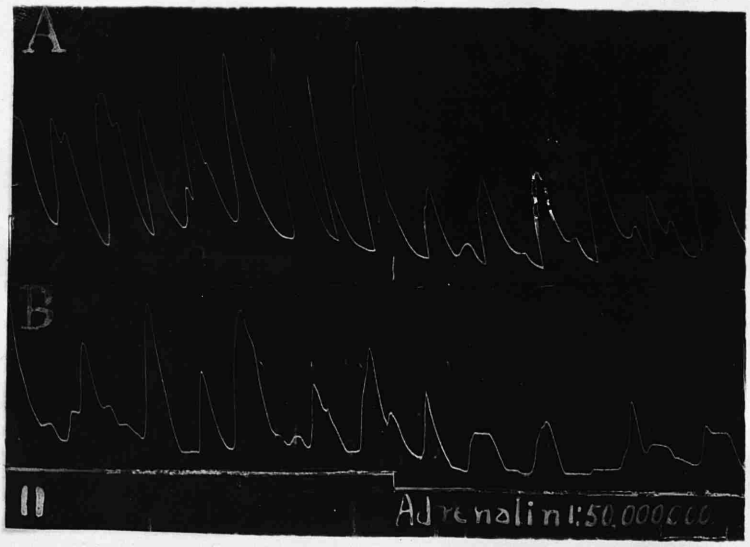


Fig. XLVIII

FIGURE XLIX.

Non-pregnant Uterus - Rat (210 grms).

The effect of Atropin 1:1000 after Pilocarpin 1:2000 upon the non-ganglionated horn - 1" long.

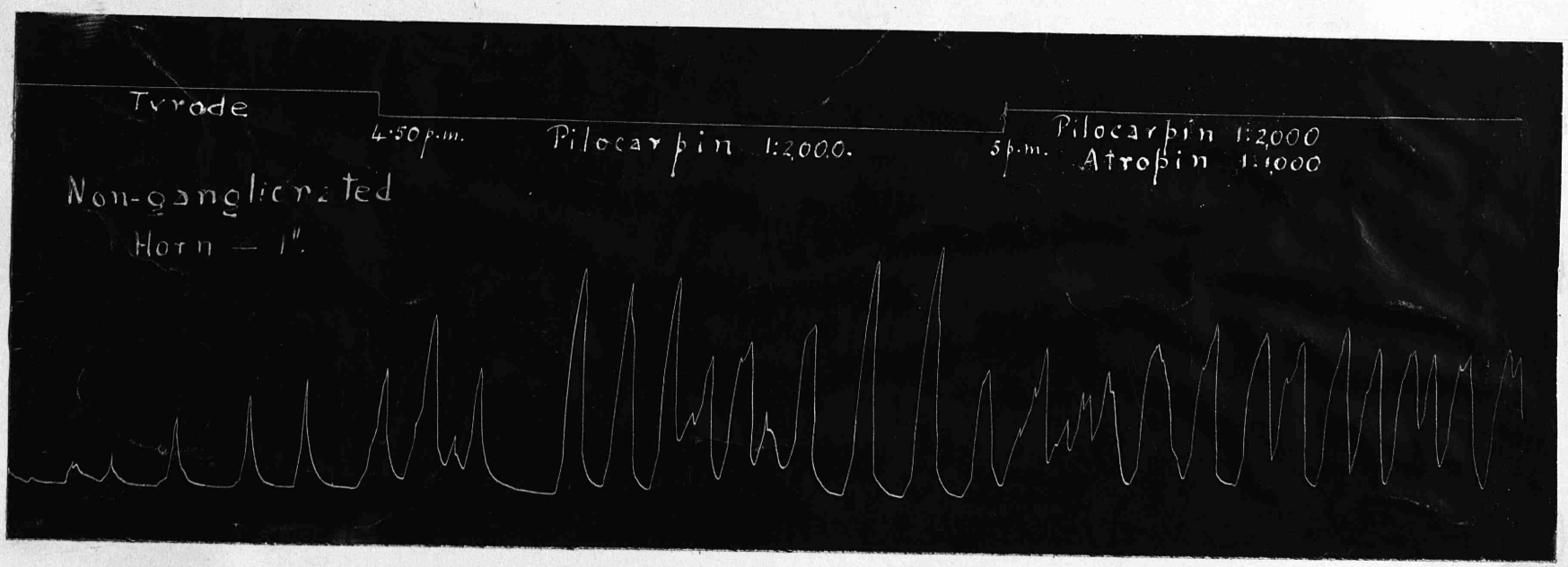

Tyrode
4·50 p.m.
Pilocarpin 1:2000.
5 p.m.
Pilocarpin 1:2000
Atropin 1:1000
Non-ganglionated
Horn — 1".

Fig. XLIX

FIGURE L.

Non-pregnant Uterus - Guineapig (470 grms).

Effect of Atropin 1:1000 after Pilocarpin 1:2000 upon the non-ganglionated horn.

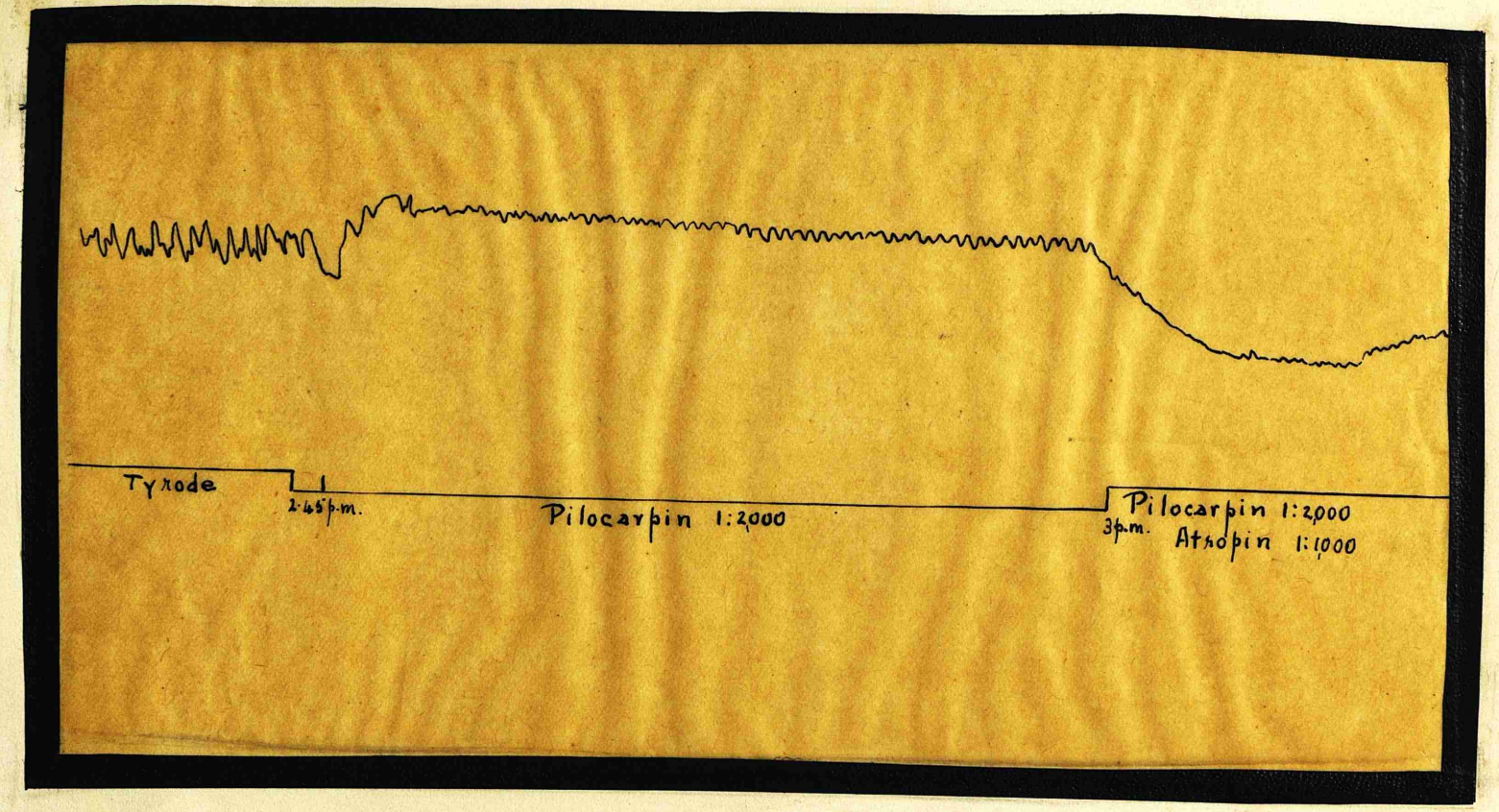

Tyrode
2·45 p.m.
Pilocarpin 1:2000
Pilocarpin 1:2000
3 p.m.
Atropin 1:1000

Fig. L.

FIGURE LI.

Non-pregnant Uterus - Rat (225 grms).

The effect of Atropin ;:500 after Physostigmin 1:1550 upon the non-ganglionated horn.

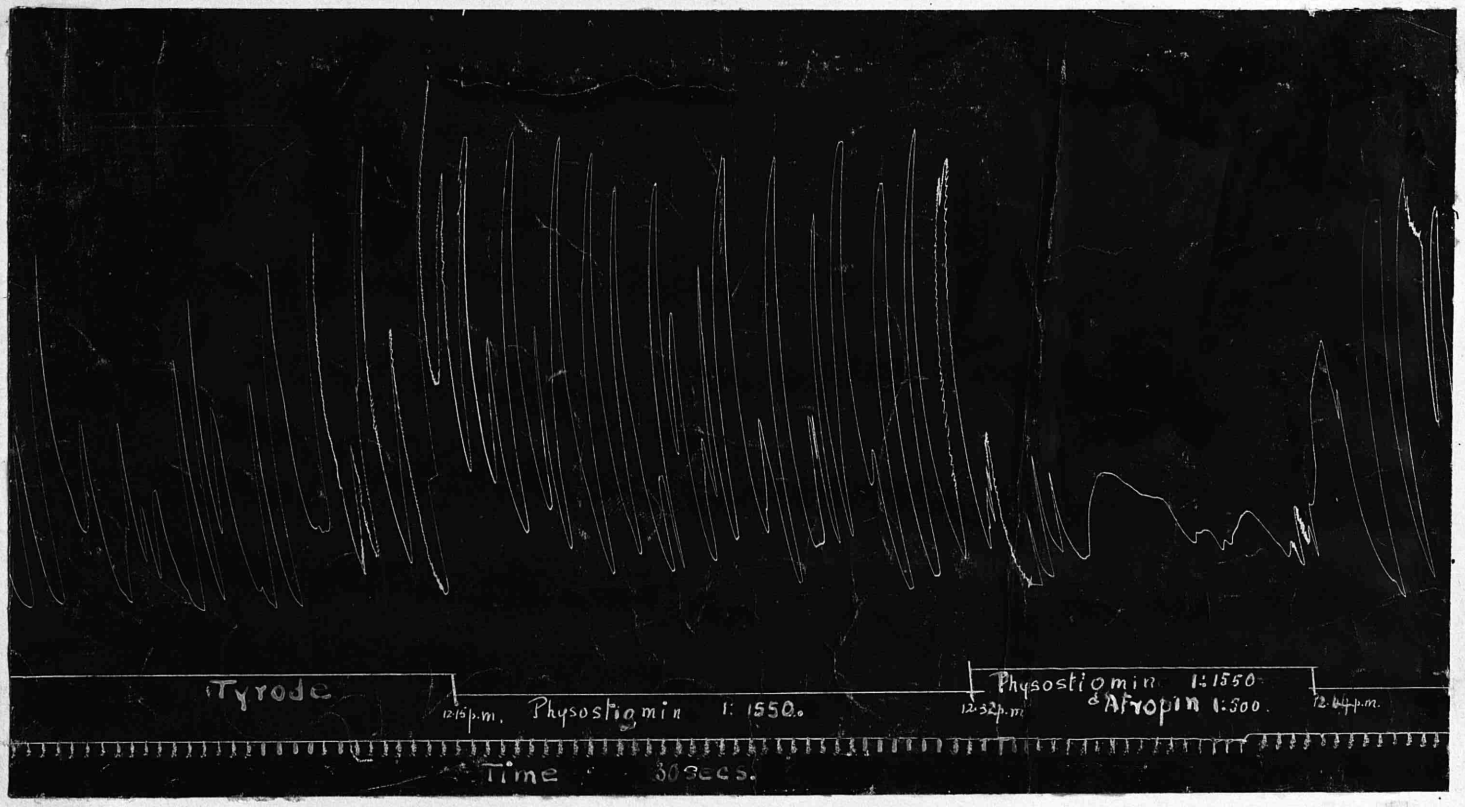

Tyrode
12.19 p.m. Physostigmin 1: 1550.
12.32 p.m.
Physostigmin 1:1550
& Atropin 1:500.
12.44 p.m.
Time 30 secs.

Fig. LI

FIGURE LII.

Pregnant Uterus - Guineapig. (590 grms).

The effect of Atropin 1:830 after Physostigmin 1:4600 upon the non-ganglionated horn.

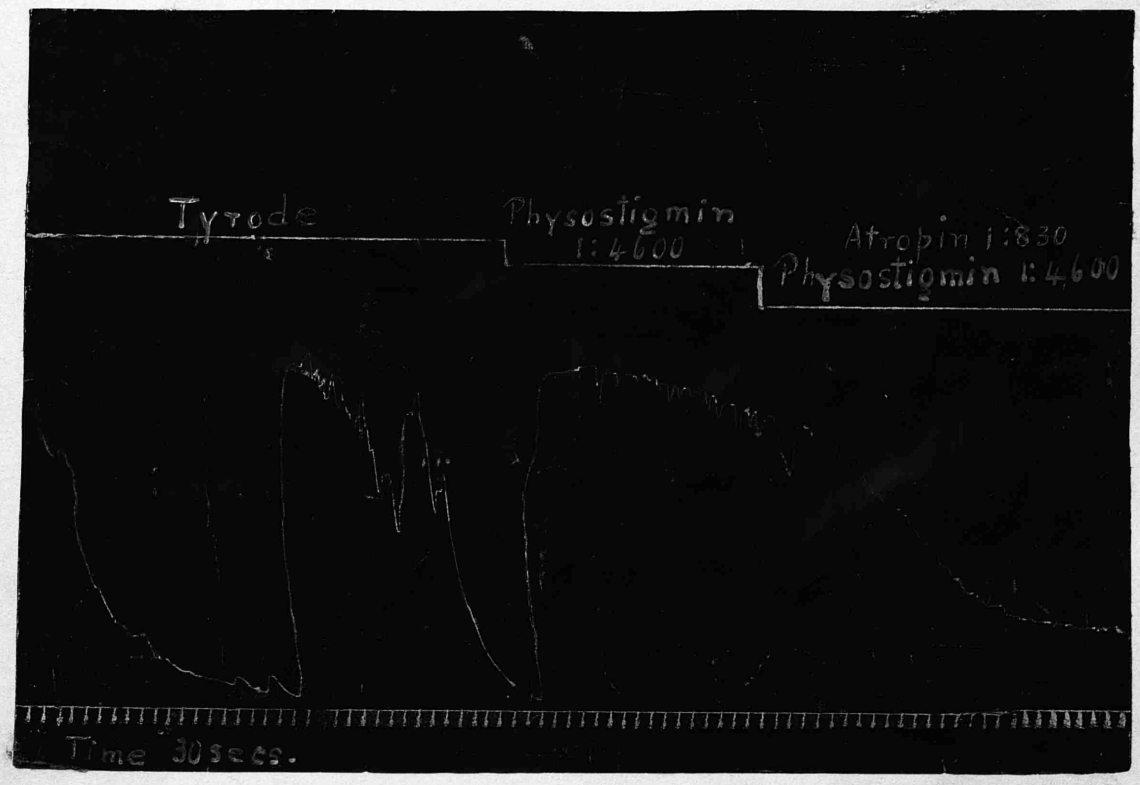

Tyrode
Physostigmin
1:4600
Atropin 1:830
Physostigmin 1:4600
Time 30 secs.

Fig. LII

FIGURE LIII.

Pregnant Uterus - Guineapig (600 grms). Comparison between the effect of Adrenalin 1:250,000 upon

(A) the non-ganglionated portion and

(B) the ganglionated portion comprising the uterine end of the horn and the cervix.

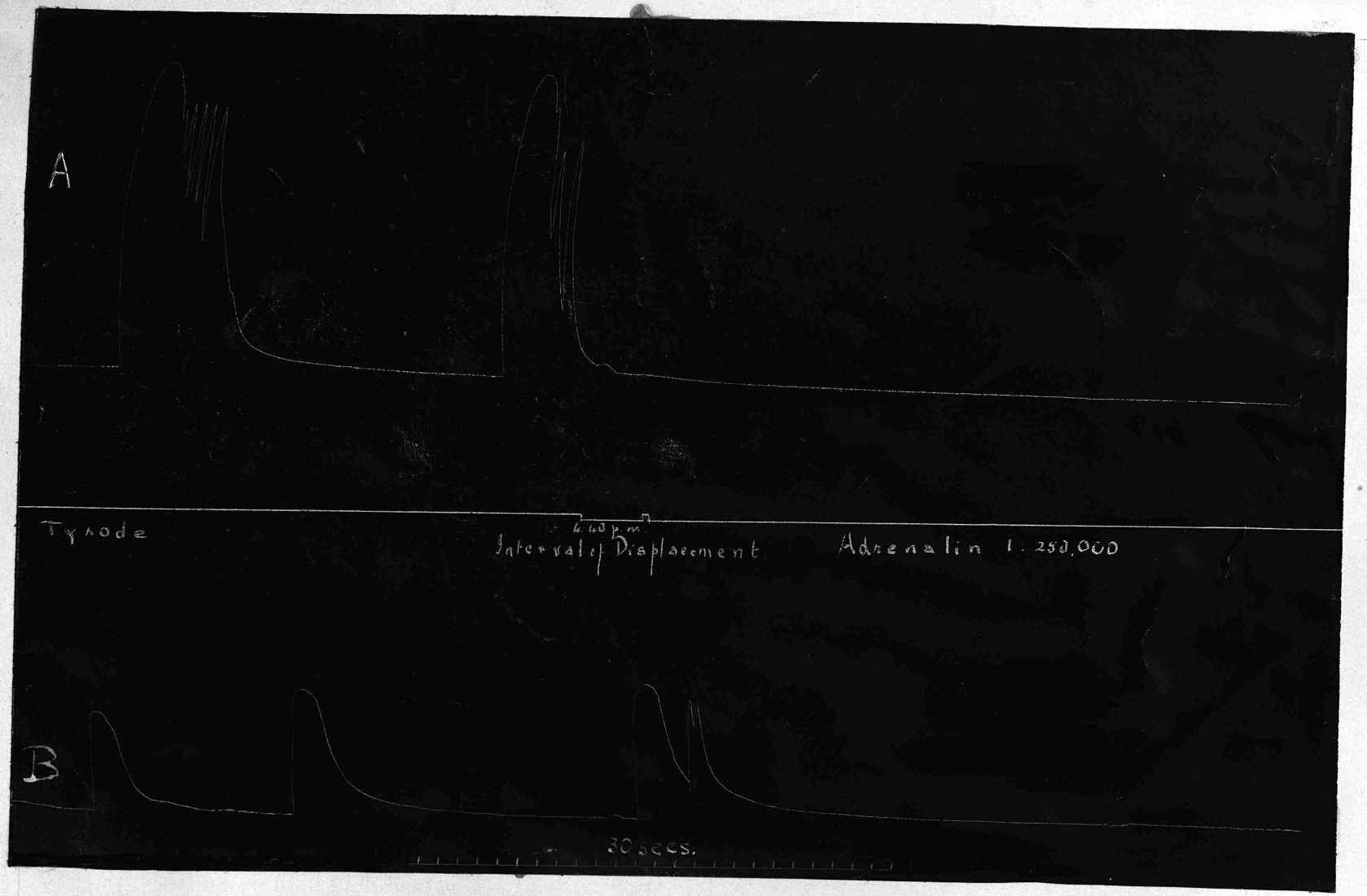

A
Tyrode
4.40 p.m.
Interval of Displacement
Adrenalin 1. 250,000
B
30 secs.

Fig. LIII

FIGURE LIV.

Non-pregnant Uterus - Guineapig (600 grms). Comparison between the effect of Adrenalin 1:166,700 upon

(A) a portion comprising the uterine end of the horn and cervix with the ganglion and

(B) a portion of the ovarian end of the horn unattached to the ganglion.

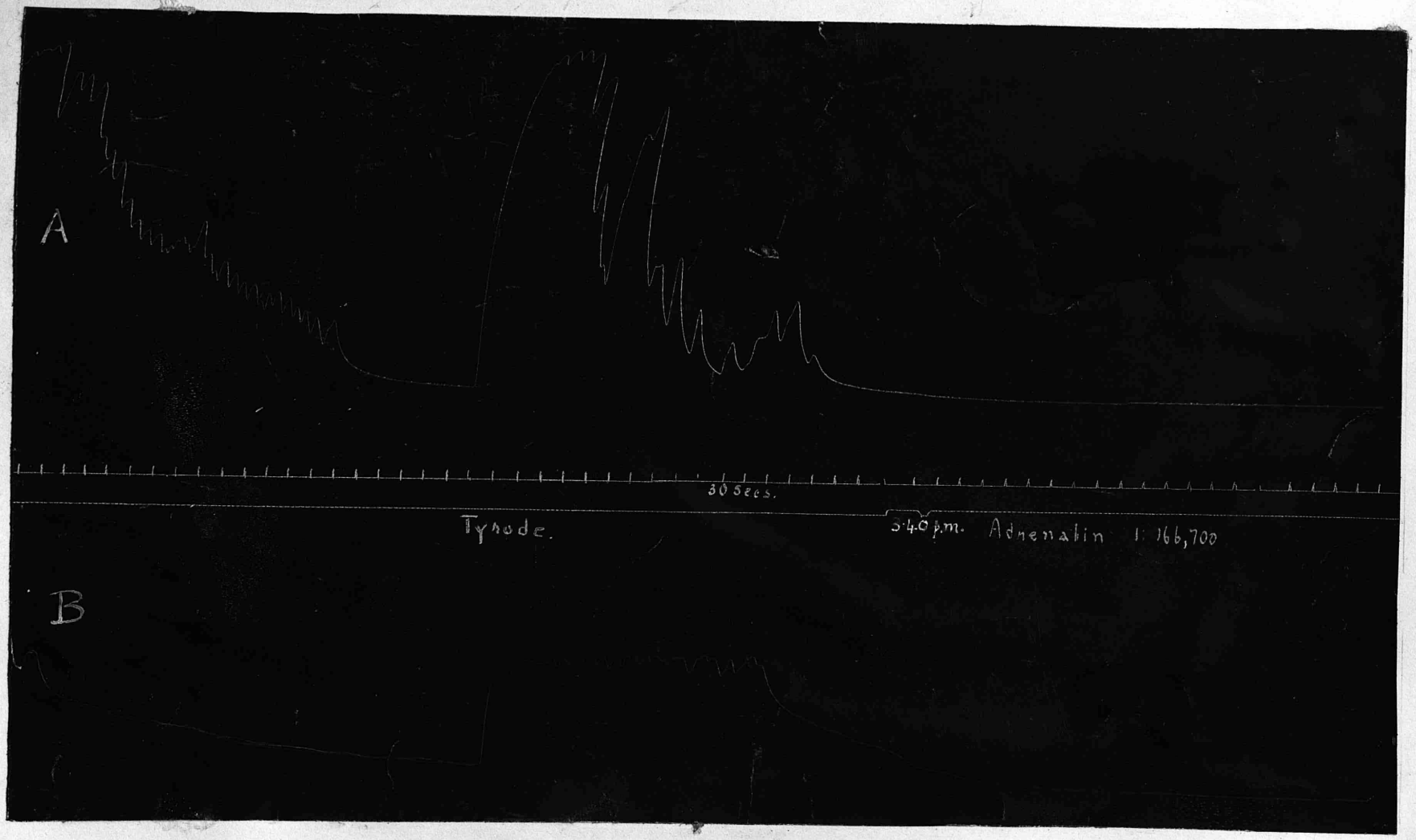


Fig LIV

FIGURE LV.

Diagram showing three possible levels on the neuro-muscular chain at which drugs act to modify the movements of the excised uterus.

s. nerve station.
n. nerve ending.
r. receptor substance.
c. contractile substance.
+ augmentor) fibres of the hypogastric
- inhibitor) nerve.

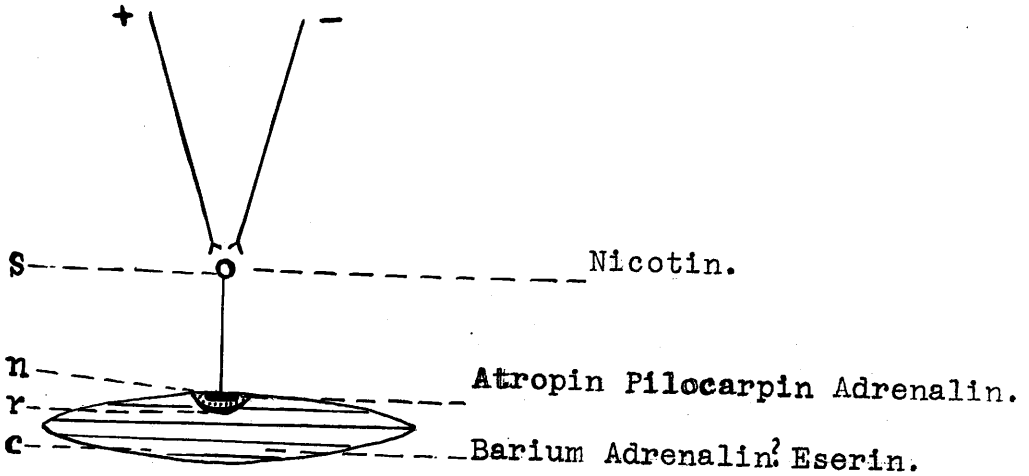

+
−
S
Nicotin.
n
r
c
Atropin Pilocarpin Adrenalin.
Barium Adrenalin? Eserin.

Fig LV