THE PITUITARY BODY

THE THERAPEUTIC VALUE OF THE INFUNDIBULAR EXTRACT IN SHOCK, UTERINE ATONY, AND INTESTINAL PARESIS.

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Two years ago I had the honour of reading a paper before the Liverpool Medical Institution on the calcium metabolism, with special reference to the ductless glands and the female genital organs; and I then indicated some of the lines on which our work was being carried out, and hinted at the results already obtained in regard to the pituitary body. An account of the experiments was published by Dr. Hinch and myself up to the end of July, 1906, and was published in the British Medical Journal early in this year; and although in these papers it was pointed out in what way clinical applications were possible, I have often been asked if we had got any results of practical value. It is for this reason that I now record some of the clinical results dependent on a small portion of that work—namely, the therapeutic value of the extract made from the infundibular portion of the pituitary body.

HISTORICAL.

During the first half of the last century, before the spirit of experimental inquiry in regard to medical problems became the rule rather than the exception, it was the custom to relegate to the lumber room of scientific knowledge those portions of the human anatomy the functions of which were not apparent. Further, they were “dumped” in the corner reserved for “evolutionary” or “rudimentary” relics.

Now a little consideration, quite apart from experimental investigation, might have led to a very different attitude in regard to some of these structures. For it is self-evident that we have no right to regard as rudimentary those portions of man’s anatomy which present, when submitted to a very casual naked eye and microscopic examination, if not a higher and more complex formation than is seen in the lower animals, at least one that is of equal development. In connexion with the structure under discussion, I may point out that there is little, if any, development of the posterior portion of the pituitary body in elasmobranchs, whereas it is well developed in the higher mammals and in man.

It was not until 1894 that the wonderful properties of the extract made from the adrenals were described by Oliver and Schäfer. In 1895 these workers investigated also the physiological effects produced by an extract made from the pituitary body, and certain other extracts, such as those made from the spleen and thyroid. While adrenalin sprang into fame, the pituitary body, which undoubtedly deserves a nimbus of its own, remained with its light hidden beneath the very brain that should have recognized its virtues.

ANATOMY AND DEVELOPMENT.

The pituitary body situated at the base of the brain in the depression of the sphenoid bone, known as the sella turcica, is a small rounded organ, and consists of two parts—an anterior lobe (hypophysis), which is the larger, and more or less encloses the posterior (infundibular) lobe. This posterior lobe is connected with the outer aspect of the floor of the third ventricle by the stalk known as the infundibulum (Figs. 1 and 2).

Structurally the anterior lobe somewhat resembles the fetal thyroid, and consists of an irregular glandular organ composed of cubical or polygonal epithelial cells which are separated by connective tissue richly supplied with blood vessels. The posterior lobe, which is divided from the anterior by the epithelial cells of the pars intermedia, is of a totally different composition, and consists of a ground-
of passing notice. The anterior lobe, whose structure so much resembles that of the thyroid gland, arises from the stomodaeum, and becomes isolated in close apposition with the base of the fore-brain. The pars intermedia is derived from the same source.

In passing it may be mentioned that the thyroid gland is developed from an outgrowth from the primitive pharyngeal cavity, and its epithelial elements are, therefore, hypoblastic in origin.

The pars nervosa of the pituitary body is formed by a downgrowth from the floor of the third ventricle. This downgrowth expands at the extremity (posterior lobe) where it comes into relation with the anterior lobe, and remains connected with the brain by the hollow stalk which, as already stated, is known as the infundibulum. The infundibulum and posterior lobe should be called by the inclusive name "infundibular body." In some of the lower animals, such as the cat, a cavity may be seen in the posterior lobe directly connected with the third ventricle, and it must be understood that there are certain morphological peculiarities in different mammals.

P. T. Herring9 has studied the histology, comparative anatomy, physiology, and development of the pituitary body.

**Physiology.**

Until quite recently very little was known definitely upon this subject.

The physiological functions of a structure such as the infundibular body are studied in two ways:

1. By injecting an extract of it into another animal.
2. By noting the effects produced by the removal of the whole, or a portion, of the structure under investigation.

In regard to the second point, it has been shown by Panunco6 and Harvey Cushing,9 and others that total removal of the pituitary body from animals inevitably leads to death. Further, it has been shown that the removal of the anterior lobe, or of a portion of it, leads to the condition almost invariably associated with destructive pituitary disease.

There is still much to be learnt, however; and as Dr. Hick and I are now engaged upon work in connection with the correlation of the ovaries and other ductless glands, I do not propose to anticipate, but pass on to the first point mentioned above—namely, the results of injection of the extract. In 1895 Oliver and Schäfer7 found that an extract made from the pituitary body—that is, from both the anterior and posterior lobes together—caused a rise in blood pressure, but they considered that the action was not so powerful as that of the adrenal extract, the properties of which they had previously discovered. Subsequently Hick6 found that the posterior (infundibular) portion which possessed this property, and that an extract from the anterior portion (hypophysis) alone did not raise the blood pressure. This was subsequently confirmed by Schäfer and Vincent.9 Schäfer and Magnus10 also discovered that the extract of the infundibular body produced the flow of urine by reason of a selective (vaso-dilator) action on the vessels of the kidneys.

All that came out of these important experiments was that an extract of the pituitary body was put upon the market, in the form of a compressed powder, as a diuretic. As far as I can learn it was little used, if at all.

Three years ago it occurred to me, while working on the physiology of the female genital organs, to try among other things, the influence of the extract of the infundibular body on uterine contractions. I wrote to Messrs. Burroughs, Wellcome, and Co. for a supply, and they very courteously put me in communication with Mr. H. H. Dale, who made for me a large quantity for intravenous injection. At the same time he informed me that he had already found that the infundibular extract caused uterine contractions. So that, although we independently presumed this property, he was the first to test it. His experiments illustrating the fact was, however, buried in a paper on ergot,11 and no suggestion was made to use it clinically. The effect of the infundibular extract upon the uterus is, of course, a more or less natural corollary to Oliver and Schäfer's experiments on the blood pressure.

In the course of the numerous experiments carried out by Hick and myself, which have already been published,6 we discovered a further property—namely, the action on intestinal muscle—which I shall mention directly.

**Experimental and Clinical Results.**

Having, then, satisfied myself as to the clinical possibilities of this preparation, after consultation in regard to dosage and other minor points with Mr. H. H. Dale, I asked Messrs. Burroughs, Wellcome, and Co. to supply me with the infundibular extract for clinical use. Except as a diuretic in the form of a compressed powder, to which I have alluded, no one appears to have used it previously.

I will mention in order some of the valuable properties of infundibular extract, and illustrate them from our experiments as well as by clinical records. There is no doubt, I think, that any one of these properties is sufficient to secure a permanent place in therapeutics for this much neglected portion of our anatomy.

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Fig. 4.—Vertical section through head of rat embryo, showing the formation of the two parts of the pituitary body (diagrammatic). TH, Thalamencephalon. P., Pineal body. PH, Cerebral hemispheres. N., Part of nasal cavity. MB, Mid-brain. BB, Hind-brain. PB, Cervical part of pituitary body. PP, Recess part of pituitary body. SG, Fourth ventricle. (Young and Robinson, Cunningham’s “Textbook of Anatomy.”)

Fig. 5.—The effect of infundibular extract upon the blood pressure and pregnant uterus in the rabbit.
1. Infundibular Extract Raises the Blood Pressure.

This property, as already pointed out, was first discovered by me and Schifer, but I am now in the conclusion that the infundibular extract was not so effective as adrenaline; this, however, is not the case. Infundibulin, if I may call it so, is remarkably like adrenaline in this respect since sometimes it raises the blood pressure better when the animal or subject is in a condition of shock than in normal circumstances. Most of our own experiments were carried out in pithed rabbits, in whom the blood pressure falls to a very low level. I look upon this as a most valuable collateral addition to its action: this raising of blood pressure in conditions of shock to a greater degree than is possible in normal circumstances of course.

Further, infundibulin keeps the blood pressure raised for several hours. This fact, too, can hardly be overestimated. We know how fleeting is the effect of adrenaline, and how useless, therefore, it is in cases of shock. In this new preparation, however, we have just the agent we need for the treatment of this condition.

In the case of a patient under the care of my colleague, Mr. Jean Ream, it happened, for instance, that I was called upon to treat a patient suffering from an acute condition; I have myself used infundibular extract in cases of shock on several occasions. A good instance was the following case:

P. S. I removed a large fibromyomatous uterus which was firmly adherent to the bowel and was fixed in the pelvis by adhesions to existing peritoneal adhesions. After the operation, which was one of extreme difficulty, the patient was put back to bed with no pulse to be felt at the wrist; infundibular extract had been given before she left the table, and continuous subcutaneous salines were administered when she reached her bed. She made an excellent recovery.

I must emphatically point out here that this drug must in no way supersede, nor take the place of, salines infusions. It is used to raise the blood pressure for the time being, and in this way to save the patient during the critical period of post-operative breakdown, a condition which salines cannot affect. I do not think the case just mentioned would have recovered on salines alone. On salines infusions, however, rests the responsibility of maintaining any improvement produced.

While our papers on the experimental results which we had obtained were in the hands of the editor of the British Medical Journal, Lockhart Munnery and Sydney pig-bag experiments were made upon the blood pressure in reference to shock, and concluded in regard to the extract of the infundibular body that our present knowledge of its properties and dosage was too incomplete to make it advisable to use it upon the human subject, without, however, that the results that my colleagues and I have obtained at the Royal Infirmary will dispose of that view.

2. Infundibular Extract causes Powerful Contractions in the Pregnant, Puerperal, and Menstruating Uterus.

I have already said that it is somewhat natural to infer such an action in view of the effect infundibular extract has upon the blood vessels; at the same time, I would point out that the presence of substance in the blood vessels, and its action upon the blood vessels, is more specifically upon the uterine vessels than upon the uterine. Consequently, we were very glad to find that infundibular extract had a very special action on uterine muscle. Fig. 5 illustrates this effect upon the pregnant uterus of a rabbit.

When, therefore, I proceeded to use the extract clinically, my anticipations were specially realized, for not only are the contractions in the human uterus made more powerful, but they are more prolonged than are those produced by any other preparation, not excluding the extremely active forms of hormones.

Not a large number of serious cases have presented themselves. In normal labour I have used it with the desired results, but it is in the serious cases that one washes for assistance. In two cases of Caesarean section I had the opportunity of observing the naked-eye effect of a single injection; it is immediate and convincing. The uterine contracts into a blanched "ball," and only relaxes subsequently to a moderate degree. Subsequent swallowing of the uterus, due to defective contraction and retraction, is one of the dangers consequent to a Caesarean section, especially if performed before the onset of labour; infundibulin, in the presence of widespread blood clotting, and blood clots that are retained and become infected—a state of affairs favoured by any contraction of the pelvis which may be present, for this condition leads to the sagging forward of a survoluted organ.

Too, then, those are those cases of sudden and serious haemorrhage which may occur before, during, or after labour. I supplied some infundibular extract to Dr. Horsey, the late obstetric assistant to this hospital, in a report that he would give it an impartial trial. I cannot do better than append his report:

I used infundibular extract in two cases, and Dr. G. F. R. Smith used it in one other. In regard to the latter, which was a case of post-partum haemorrhage, Dr. Smith said to me on his return, "What do they need anything better than ergot for? the lot I injected acted like a charm." I knew, however, that there was no ergo in the bag, so I asked him to show me the box he got it from, whereupon he produced the infundibular extract.

In another case of post-partum haemorrhage, when I used it in conjunction with massage through abdominal walls, bleeding stopped in about three or four minutes.

The following are brief notes of the third case—one of placenta praevia—in which this preparation was used:

C. S., aged 29, 4 para. Her second and third deliveries were complicated by adherent placenta, and membranes. In present pregnancy bleeding began during the eighth month. A severe haemorrhage—five pints of blood clots were removed from the "chamber"—occurred on July 23rd, 1908. On my arrival the active bleeding had ceased, but the uterus was quite flaccid and no pains were occurring. The os uteri admitted three fingers, and the placenta was felt to be overlapping the uterine orifice, and extending 1 in. beyond the cervico-marginal line. The membranes were ruptured, version performed, a leg brought down, and infundibular extract injected. Two pints of saline solution were also infused intravenously. Pain came on about thirty minutes later without further haemorrhage. A second dose of the extract was then given, and the patient, whose condition had considerably improved, was removed to hospital. A dead child was born spontaneously three and three-quarter hours after the pains had recommenced—that is, four and a quarter hours after the first injection. Subsequent contractions and retraction were good, and the patient made an excellent, but slow, recovery.

There is little doubt that this preparation acts on the atomic uterus as well as if not better than, it does upon the contracting organ, just as it does upon the blood vessels in conditions of shock.

I am inclined to think, therefore, that in the future we shall rely on infundibular extract to produce contractions of the uterus in many serious obstetric complications and difficulties, although I should, perhaps, add that in my opinion it ought not to be given before labour. I have for some time carried it in my obstetric bag, and would not willingly be without it.

3. Infundibular Extract Acts upon the Intestinal Muscle.

During our experiments on pithed rabbits we observed that violent peristaltic movements were generally set up in the intestines. On more than one occasion this led to the expulsion of faeces. Fig. 6 gives a very good illustration of the effect of the blood pressure of the intestine in movements; and it shows how violent they must have been to cause such rises in the general blood pressure.
With our eyes always open to the possibility of practical and clinical results, it is once occurred to us that specific cases of paralytic and distended intestines might be obtained.

It requires no pen picture of mine to remind surgeons what it means to try to treat the peritoneal cavity of the terrible battles that are often waged against this dangerous and obstinate complication; nor obstetricians who have encountered the difficulties of pseudo-ileus after Caesarean section, even after normal parturition. Most of us can recall vividly each case we have met with, for they are often indelibly impressed on our minds by the hopeless position in which we have been placed. I know there are surgeons who will say that for these cases we were treated early enough with calomel and turpentine enemata, there should be no difficulty. While that is, of course, the sound and absolutely correct as advice, most of us know that the sequel is not always encouraging. Besides, in gynaecological work especially—an enema cannot always be safely given, owing to lacerations or perforations in the rectum.

I would invite those, therefore, who cannot effect relief in any other way—if they be too sceptical to use it earlier—to give a trial to infundibular extract. I have now used this extract for intestinal paralyis in a fair number of cases, with modern methods this complication is not so common as it used to be—and I have never known it to fail.

Again, let me point out that, as with the blood vessels and other intraperitoneal extract groups to set out correctly, certainly when there is considerable atony and paralyis than in normal circumstances. Indeed, when the patient is not distended, and when peristalsis is normally present, an effect is not always observable; but not say it is not present, but the result is not so obvious. This is no reason, however, why the extract should not be given early. It should be given as soon as the patient is received.

I do not propose to record my own cases, for independent evidence is of more value; but, as I have already said, I have personally never known it to fail. It is interesting, also, that in some of the cases in which I have given it to combat shock or collapse after a serious operation, flatus has been passed per rectum during the first twelve hours—a happy state of affairs which all will agree hardly ever occurs in ordinary circumstances. It happened in the case of shock I have already referred to.

I am indebted to several of my surgical colleagues at the Royal Infirmary for having sufficient faith in my recommendations to test the extract in some serious cases of paralytic distension. As I think that the evidence of unbiased observers will probably be more convincing than mine, I will send a few illustrative cases as recorded for me by my house-surgeons.

Mr. A. M. Roberts has sent me the following account of a very serious private case under the care of Mr. Paul.

Case I.
August 23rd, 1909. K. W., aged 11. Admitted for acute appendicitis. Immediate operation; free fluid and pus evacuated. Fowler’s position adopted, with rectal saline, one pint every two hours. Subsequently continuous saline infusions into the thighs. Pulse rate 135; respirations 32. August 24th. Next morning the patient was slightly better. Pulse rate 116; respirations 24. Later in the day the patient became worse; the pulse rate rose to 160 and respirations to 40. The following day the patient was very ill and becoming much distended. Infundibular extract was administered at 5.35 p.m.; an evacuations of the bowels occurred in ten minutes. Next morning the patient died suddenly. Post-mortem examination revealed pneumonia of the right lung. The effects of the infundibular extract on the blood pressure: The blood pressure rose steadily for twelve hours, and only subsided five hours before death. The temperature also continued to rise; no necessarily as the result of the extract, but more probably owing to the onset of pneumonia.

Mr. Tinsley has given me the following report of two cases under the care of Mr. Jeans.

Case II.
July 31st, 1909. The patient had a severe attack of vomiting and pain. He was then fairly well for a month, but very constipated, and had to take pills and enemis emesis. July 30th. The bowels were well moved.
July 31st. No motion.
August 1st. Very slight motion.
August 2nd. No motion, although he had taken pills and used an enemis. Some pain towards evening and a severe attack of retching. One ounce of castor oil given. This and a second dose were at once returned.
August 3rd. Admitted to the Royal Infirmary. Immediate operation—ileo-sigmoidostomy—was performed, an obstruction having been found in the transverse colon. Calomel (gr. 2) was given, with no result. No dysentery in the rectum was equally ineffective.
August 4th. Same treatment, with no result.
August 5th. Morphine (gr. 1) and calomel (gr. 6) were given, with no result. Subcutaneous saline infusions were also administered. The patient was vomiting continually, was distended, and in great pain.
August 6th. Right lumbar colotomy; more calomel given, with no result.
August 8th. Absolute obstruction had now existed for five days. Vomiting was continuous and he was in great pain from flatulence and distention. Calomel, aqua ment, pil, and caesuget physic and various other drugs were given, without relief. Further, an injection of infundibular extract was given into the muscles of the forearm. Within five minutes a great prandial evacuation of flatus was passed by the colotomy wound, with instant relief. In an hour a second injection was given, and again within five minutes a liquid motion was passed by the colotomy wound.

August 7th. The bowels acted slightly, naturally, through the colotomy wound. Vomiting continued much, but the patient did not appear to suffer. The patient got distended again, and was in great pain. Another injection of infundibular extract was given, which, within five minutes, a profuse motion, and the passage of flatus both by the rectum and by the colotomy wound. There was no relief.
August 9th. Much less vomiting. In the evening the flatulence returned, when a fourth injection of the infundibular extract was given, with a result similar to that during August 7th.
August 9th and onwards. From this date the patient has improved steadily, and the bowels have given no further trouble.

Other Effects Noticed.—The pulse tension went up considerably for four nights following the injection of the extract; the patient was allowed to take food and water in sufficient quantities, and was also allowed to take cold water without difficulty. On the 4th the pulse rate was 100, and the temperature normal. The patient improved steadily, and the bowels gave no further trouble.
are other surgeons present to-night who, having heard of the value of the extract in our hands, have given it a trial. I shall be much indebted in hearing further evidence in regard to it."

I myself venture to think that in infundibular extract we have at last found a reliable agent for the treatment of paralytic distension of the bowel. If an extended trial this prove to be the case, every surgeon's anxieties will be considerably lessened, to say nothing of the lives that will be saved. I have not yet tried infundibular extract in post-operative acute gastric distension, but I should not be at all surprised to find that it would prove to be of real value in this very serious, if somewhat rare, condition.

4. Collateral Effects.

I now come to some collateral effects produced by the infundibular extract which are extremely important; and it is just these additional effects which put this preparation so far ahead of adrenalin, apart from its greater efficiency and more prolonged action on the involuntary muscle fibres, already discussed. I refer to its special action on the heart and kidneys. This extract, after a short initial increase in the frequency, slows the heart and causes more powerful contractions. This effect is still produced, though to a less degree, with the patient under the influence of atropine, which is the therapeutic equivalent to severance of the vagi. In similar circumstances adrenalin causes acceleration.

Again, while adrenalin causes a diminution in the secretory power of the intestine, has, as already mentioned, a marked diuretic effect which is of very great post-operative value.

Finally, if we may say for the benefit of chemists, laryngologists, and oculists, that infundibular extract may prove to be more effective than adrenalin in producing local anaesthesia. I do not wish to speak positively upon this point, as only one or two experiments have been conducted on this view, but they seem to support this view.

I have no time to touch on the preserves of the general physician. I am sure, however, that before long there will be many who will use it in asthma and many other conditions.

**Mode of Action, and Nature and Origin of the Active Principle.**

Without going too deeply into the subject, I may, perhaps, be allowed to say a few words as to the manner in which infundibular extract acts. There is little doubt that its chief effect is peripheral, for if we place a rabbit's isolated and active uterus in Ringer's solution, we find that the contractions instantly become weaker, and after a small quantity of the extract, I do not think that we have any evidence to show that infundibular extract acts on the "pressor centres"; but this is quite possible, and, if so, is an important fact in the case of the asthmatic or heart condition of these controlling structures.

Probably it will not be long before the active principle is isolated, for much good work has been done on the subject of "pressor bases" in the last few months. It may, therefore, not be without interest to recount, very briefly, the present position in regard to these compounds.

In 1906 Aboeiasa showed that a rise in the blood pressure was produced when the extracts made from putrid meat were injected into the blood stream. This year Barger and Walpole published a paper in which they described the identification of the "pressor bases" concerned. These observers found that they were anilines, namely, phenylethylamine, p. hydroxyphenylethylamine, and isoamylamine. There are one or two practical points arising from these chemical investigations. First, Rosenheim was able to show that the active principle of the placental extract of Dixon and Taylor, which was thought by them to be the cause of the normal uterine contractions in labour, was produced by inipotent pectoral in the placenta used, and contained the amines already mentioned.

Next, Barger and Dale, a few months ago, showed that the pressor properties of ergot are also due to these same bodies, which is well known; it is thus possible to account for the "pressor bases" as organic compounds which cause a rise in the blood pressure when injected into the blood stream.

**A distinct relationship to adrenalin in regard to their structural formula.**

The following structural formulae are given by Dixon and Dale:

\[ \text{CH}_3 \text{CH}_2 \text{CH}_2 \text{NH}_2 \text{ISOAMYLAMINE} \]

\[ \text{OH} - \text{CH}_2 \text{CH}_2 \text{NH}_2 \text{HYDROXYPHENYLETHYLAMINE} \]

\[ \text{OH} - \text{CH} (\text{OH}) - \text{CH}_2 \text{NH}_2 \text{ADRENALIN} \]

It is important to bear these facts in mind, for there is in them a definite promise that in the near future the chemist will be able to synthesize the active principle of the infundibular body.

At present, however, we have to rely on an anatomical structure to provide us with it. So that it is interesting to know—or, perhaps, I should say conjecture—by what elements in the infundibular body the active principle is produced. In Fig. 3, representing a high-power view of the pituitary body, we see that in the infundibular portion, in addition to the nervous elements, there are islets of epithelial cells, as I have already described. It is probably these epithelial cells that contain the active substance in the body, and it is this that has hitherto been called the "secretory part" of the gland. It is from these epithelial cells that the body is released and enters the blood stream, and it is here that the adrenalin-like principle is produced. For there is absolutely no question of its being an extract from the brain, for there is no secretion of the gland that enters the blood stream. The active substance is therefore produced from the glandular epithelium of the body, which is similar in form and function to the corpuscles in the kidney and the lung, and which is released as the body is produced.