THE VALUE OF PITUITARY EXTRACT

– on –

THE TREATMENT OF

U T E R I N E D I S O R D E R S

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H. MACINTYRE, M.B., C.M.

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

THE VALUE OF PITUITARY EXTRACT IN THE TREATMENT OF UTERINE DISORDERS.

INTRODUCTION.

From remote times in the history of medicine, tissues and organs of animals have been used in the treatment of disease with little more than Empirical Knowledge or superstition to support their claims to merit. During recent years there has been a revival of interest in Organo-therapy and many new preparations - especially animal preparations, have been brought before the profession for the treatment of disease, prominent among them, uterine disorders.

Brown-Sequard contended that all the glands give, by internal secretion to the blood, principles essential to the general good health of the body. This is shown if all thyroid tissues be removed, death invariably ensues due to arrest of secretion, yet if that secretion be in excess, a disturbance of the normal or healthy condition of the individual is the result. Experiment and clinical experience have shown that the administration of extract of other glands counteracts this deleterious effect, acting as anti-toxins, and so re-establishing the normal balance. Notably among these glands is the extract of the infundibular portion of the pituitary body, which is now known by such varied names as pituitrin, infundibulin and the like.

It would appear that these glands so work in groups that their secretions in health balance each other and function or act as toxins and anti-toxins. If one gland or group gets the upper hand and the opposing gland or group of glands fails to respond, there is excessive formation of a toxin whose normal antidote is deficient and the symptoms are the effects of this toxin. An account of the experiments with pituitary extract which have been carried out by Hick and Blair Bell in the British Medical Journal in February and March 1909, and later (Dec. 4, 1909) some of the clinical results, following on these experiments, were published in the same journal.

That the pituitary body produces internal secretions necessary to life and good health is certain, for removal is followed by a train of symptoms and eventually by death.

Little is known as to the nature of these secretions but it would appear that they exercise considerable influence on tissues which are rich in phosphorus and poor in nitrogen (bone), for it has been found (Schiff)[1] that when the extract was administered to an old man there was marked increase of phosphorus excretion by the urine and faeces whereas there was no corresponding increase in the nitrogenous metabolism. The physiological effect of the administration of pituitary extract is a decided rise of blood pressure and slowing of the pulse due to increased cardiac

contraction and arterial constriction. This effect remained after the central nervous system had been destroyed proving that the action is directly on the muscles and independently of their innervation. (Schafer and Oliver)[2].

Howell[3] and later Schafer and Vincent[4] showed that an extract made from the anterior lobe did not produce these results, but that the extract of the posterior or infundibular portion alone possessed this property. Dale[5] found that infundibular extract produced uterine contractions. Bell and Hiell[6] confirmed this and also discovered that when experimenting in pithed rabbits that violent peristaltic movements were set up in the intestines.

In uterine haemorrhages, especially at parturition, and diseases such as endometritis and uterine discharges, (leucorrhoea) this extract is an invaluable remedy.

Many of the new remedies employed in uterine disorders possess valuable therapeutic properties but before they can be of general use practically, they require to be subjected to proper clinical tests. This seems to be the only way of arriving at the proper value of a remedy. In the laboratory a preparation gives certain results, yet it is in actual clinical work that one arrives conclusively at the merit or demerit of a remedy.

In this Thesis I propose to consider one of the more important of the newer remedies, viz: pituitary extract, more especially with regard to its value in the treatment of uterine disorders.

It will be convenient to discuss first of all the symptomatology of Uterine Disorders and the following are briefly the symptoms which are present:-

(a) Pain
(b) Haemorrhage.
(c) Leucorrhoea.

Pain at some period is a symptom of all uterine disorders, though, in some cases, pain may be entirely absent throughout. Pain may be functional, that is, it may be present without apparent pathological change in the uterus or its appendages.

The methods of treatment commonly adopted are:

(1) Rest
(2) Medicinal treatment
(3) Operative "

HAEMORRHAGE.

I. In connection with Pregnancy.

(1) Abortion or miscarriage. Threatened or inevitable. It is important to remember that a patient may menstruate regularly, or rather, has bleeding recurring about every month which is taken to be menstruation while she is pregnant. This may happen for as much as five or six months. Abortion in a section of cases may be averted by rest in bed, light diet, sedatives (Bromide of Potash &c) and a daily light aperient. Should severe haemorrhage occur

labour should be induced unless, as sometimes happens, spontaneous labour sets in. In the latter condition - inevitable abortion -ergot or drug of similar action should be administered.

Under this heading might be mentioned in complete abortion or miscarriage - portions of the ovum being retained and causing bleeding; and missed abortion or miscarriage when the foetus dies in the earlier or middle period of pregnancy. Usually the ovum is expelled at no long interval, though, in exceptional cases, it is retained in utero for a considerable time after the death of the foetus. The treatment in these cases is emptying of the uterus - dilating the cervix and curetting with a blunt curette. An antiseptic intra-uterine douche is generally advisable.

Subinvolution. When the process of involution is interfered with after labour. The causes may be:-

1. Pelvic Inflammation.
2. Retention of portions of placenta or membranes after labour or abortion.
3. The presence of fibroid tumours of the uterus.
4. Passive congestion of the uterus due to getting up too soon after labour, or, perhaps, more particularly, after abortion or miscarriage.

The Symptoms of sub-involution are:

(a) Bearing down pain and backache.
(b) Menorrhagia and perhaps metrorrhagia.
(c) A yellow discharge which may be offensive.

The Signs - Uterus large on bimanual examination.

Sound passes, say, 3¼ in. to 4 in.

Treatment, generally

Rest in bed.
Hot douches
Administration of ergot
Removal of retained pieces of placenta or membrane when these are present.

In cases due to pelvic peritonitis, the usual treatment has to be applied.

Placenta Praevia. In this condition of pregnancy, the placenta is attached wholly or in part to the lower segment of the uterine wall. The two conditions are placenta praevia centralis and placenta praevia lateralis. During an advanced stage of the pregnancy - last four months or during labour - haemorrhage occurs - unavoidable haemorrhage due to separation of part of the placenta.

Treatment.

Here it is advisable to induce labour. At the onset the Vagina may be plugged with gauze; this excites contraction and arrests haemorrhage. Should the haemorrhage be severe, the os should be rapidly dilated, the hand introduced into the uterus and delivery by version performed.

Accidental haemorrhage, i.e. haemorrhage in a case of normally situated placenta. This may be concealed or external, according to whether the bleeding shows externally or not.

The cause of the bleeding is partial separation of the placenta and may be brought about by:

1. Traumatism - a blow on the abdomen or a fall.

2. Disease, e.g. Chronic Bright's disease, anaemia, syphilis, fibroids,&c.

Before labour, slight cases of this kind should, in the first place be treated by palliative measures - rest, light diet, a daily light aperient, sedatives, e.g. bromide of potash, or some form of opium. After a single severe haemorrhage, labour should be induced, but when their is extensive separation of the placenta, spontaneous labour usually occurs unless the uterine muscle is paralysed as the result of over-distention.

Post Partum Haemorrhage, - Haemorrhage which occurs after delivery, immediately or a few hours after labour is over. Haemorrhage occurring after the first of the puerperium or later is called secondary post partum haemorrhage or puerperal haemorrhage.

Causation - Local, which may be regarded as the immediate causes - Uterine exhaustion or inertia, incomplete retraction or lacerations.

Predisposing - Multiparity, especially when associated with rapid child bearing, such cases being liable to secondary inertia during labour. Debility, as met with among the poor. Over distention of the uterus (twins, hydramnios), antipartum haemorrhage, Secondary inertia during the second stage of labour, protracted or precipitate labour and prolonged administration of chloroform. Incomplete retraction due to retention of placenta or portion of it or of membranes, fibroids of the uterus.

Treatment. Endeavour to restore activity of uterine muscle in cases of inertia and promote thrombosis of the torn uterine vessels. If placenta has not been delivered it should be expressed or removed with the hand or fingers. When fairly contracted, press uterus backwards and downwards, in order to express all the clots from it. A full dose of ergot should be given at the commencement of manipulation. Hot douches (118°F.) To promote thrombosis, inject iron solution or swab inner surface of uterus with similar solution.

Restorative treatment.- Inject saline solution into rectum or it may be necessary to transfuse normal saline solution into median basilic vein. Give ether or brandy if necessary. Elevate foot of bed and when restless give morphia (gr. $\frac{1}{4}$ - $\frac{1}{6}$) with or without atropine.

Extra Uterine Pregnancy. . Bleeding in these cases is rather irregular than profuse. A menstrual period may be missed, then haemorrhage comes on, during which a decidual cast of the uterine cavity may be passed. The amount of blood lost externally may be slight but persistent and of a darkish colour. The majority of these pregnancies occur in a Fallopian tube, sometimes on, or in the ovary. The escape of the ovum is generally accompanied by severe pain, sudden in its onset, often accompanied by vomiting and fainting to actual loss of consciousness from syncope.

The treatment offering a chance of success is laparotomy and removal of the tube or ovary and products of foetation and blood.

Malignant disease of the Cervix complicating pregnancy.

A woman with malignant disease may have more or less constant bleeding with or without pain or leucorrhoea for months and on examination found to be pregnant.

Molar Pregnancy)
Placental Polypus) Among the symptoms they produce is bleeding - re-discharge.
Fibrinous Polypus)

These may be expelled spontaneously or if not, the uterus should be emptied in the usual way as soon as the condition is diagnosed. Afterwards, douche uterine cavity with iodine solution or other antiseptic and administer ergot or drug of similar action.

II. Haemorrhage not directly connected with pregnancy or labour.

Malignant Disease of the Cervix.

Symptoms.-

1. Bleeding
2. A discharge, becoming offensive.
3. Pain.

Treatment.- In early cases removal of the cervix, if the disease is confined to that part, or hysterectomy if the disease has gone beyond the cervix, with removal of surrounding tissues and iliac glands if involved. In advanced cases or cases which are inoperable, the treatment can only be palliative.

To arrest bleeding and discharge, it may be of use to scrape ulcerating surfaces with a spoon and swab with pure carbolic acid or chloride of zinc. On separation of the slough thus caused, a clean surface, more or less healthy is left until there is a further advance of the disease with breaking down of the surface. Ergot or other atypic may be of use in controlling the bleeding.

To relieve pain, morphia in some form has to be administered.

Fibroid tumours or fibroid polypi of the Uterus.

Symptoms - when any are present.

1. Bleeding - menorrhagia and perhaps metrorrhagia.
2. Pain - at Menstruation.
3. A yellow discharge.
4. Pressure symptoms.

Treatment.- When the tumour is submucous or a fibroid popypus, removal.

When interstitial, if bleeding is the chief symptom: First, try large doses of ergot, the patient should be kept in bed and hot vaginal douches used. Should the symptoms (either pressure symptoms or bleeding) become urgent, the question of hysterectomy arises.

Mucous Polypi.

Symptoms.

1. Bleeding - slight.
2. A white or yellowish discharge due to cervical or corporeal endometritis.
3. Sterility (?)
4. Dysmenorrhoea.

Treatment.- Removal with tumour forceps or cutting the pedicle with a pair of scissors. The site of attachment should be curetted or touched with Paquelin's Cautery. Uterus douched with an antiseptic.

DYSMENORRHOEA.

This is essentially pain in connection with the menstrual period.

Clinically, such cases may be divided into three groups:

I. Cases where no abnormality is discoverable in the uterus or its appendages - spasmodic dysmenorrhoea.

II. Cases in which some abnormality is detected, e.g. inflammation or congestion in or around the uterus, with perhaps adhesions. This class includes cases of growing fibroid - inflammatory or congestive dysmenorrhoea.

III. Cases where some abnormality exists in the process of menstruation itself; the only known instance of this being the passage of a membranous cast of the uterus, either whole or broken - membranous dysmenorrhoea.

Symptoms - Class I. Pain, paroxysmal in character and referred to the hypogastric region. As a rule it begins shortly before the flow and diminishes or ceases as the flow increases. The pain may cause vomiting. The pain in spasmodic dysmenorrhoea is said to be due to contraction of the uterus.

Class II. Here also the pain comes on before the flow but is constant and aching in character and is relieved by the establishment of the flow. Physical examination may reveal change in size of uterus, pelvic cellulitis or perimetitis, disease of ovaries or Fallopian tubes.

Class III. The pain is colicky or paroxysmal in character and is relieved when the membrane is passed.

Treatment.- Avoidance of over exertion or exposure to cold at the period. Administration of camphor (gr.ii - iii) Ext.Bellad. gr.$\frac{1}{6}$. Potass. Bromid. with Spt. Am. Aromat., Antipyrin, Ichthyol, Phenacetin. When this fails, dilatation of the cervix may give relief.

ENDOMETRITIS OF THE CERVIX.

This may be caused by laceration of cervix or extension of vaginitis.

The chief symptom is leucorrhoea.

Treatment.- Removal of the discharge with cotton wool and application with a Playfair's probe of a solution of sulphate of copper, iodized phenol, pure phenol, argyrol &c.

Endometritis of the body of Uterus.

Symptoms:

1. Menorrhagia.
2. Body of uterus enlarged and perhaps tender.
3. Pain on manual examination or passing a sound.

Treatment.- Is generally curetting and applying tincture of iodine to the whole of the surface and washing away excess with a douche of weak iodine water.

Age of Puberty and the Menopause are usually accompanied by increased or irregular menstruation, the latter often complicated with neurotic symptoms.

Treatment has to be regulated according to the special conditions and symptoms of the case. In cases at puberty imperforate hymen may have to be dealt with. Anaemia by administration of iron, &c. Constipation by suitable treatment, hygienic surroundings, bathing and suitable clothing. At the menopause, a combination of ergot and bromide is often called for.

Ovarian tumours cause disturbance of the menstrual function.

Malignant disease of the Body of the Uterus.

Symptoms.

1. Bleeding.
2. Discharge which tends to become offensive.
3. Pain which may come on early and be very severe.

The treatment is hysterectomy when practicable.

LEUCORRHOEA.

This is a term used to describe a discharge which may come (1) from the vagina (Vaginitis) (2) the Cervix (cervical endometritis) or (3) the body of the uterus (corporeal endometritis)

In the strict meaning of the term, the discharge would be white, but it may vary to yellowish, according to the severity of the inflammation or brownish if blood-stained as in Metrorrhagia when the case is one of corporeal endometritis.

Predisposing causes are anaemia, gout, strumous condition.

Treatment.- Attention to the general health - a tonic, such as quinine and iron or arsenic and iron with aperients, fresh air and cleansing of the affected parts.

Having dealt briefly with the symptomatology of Uterine conditions, I propose in the remaining sections to discuss the value of Pituitary Extracts in these disorders.

THE USE OF PITUITARY EXTRACT.

As illustrative of the insignificant status of the Pituitary body in the literature of disease a short time back, one may look through text book after text book of pathology and medicine, without finding bare mention of the existence of such a structure.

Nor did the Thyroid Gland fare much better, for it was considered until quite recently to be of practically no importance.

More than half a century ago, Addison assigned as a cause of the disease which goes by his name, inadequacy of the functional activity of the suprerenal glands.

His theory is the most plausible and likely of any advanced and is probably correct, but years elapsed before it received general recognition. In spite of Addison's interpretation of the importance of the function of these bodies, they continued to be classed as evolutionary relics.

But with the passing of Empirical methods and the establishment of the theory of internal secretions on an experimental basis there has been a great advance of our knowledge of the physiology and pathology of the ductless glands. According to the doctrine of internal secretion, the ductless and other glands secrete specific substances which pass into the circulation and affect all the cells of the organism in their own peculiar way. Incomplete and

scanty though our knowledge at present is, we have already learned that the ductless glands occupy a most important place in the regulation of the health of the body. If, through disturbance of a gland, there is increase or diminution of its secretion, a disturbance in other tissues is produced. Different observers have proved by the removal of the thyroid and suprerenal glands that their structures are necessary to life.

Modern organo-therapy is based upon the assumption that where the diseased human organ is no longer able to produce its normal secretion, it is possible by the use of preparation from the corresponding organs of healthy animals to supplement the deficiency. The condition known as Cachexia Strumipriva (operative myxoedema) which is brought about by the removal of all thyroid tissue is an artificially induced myxoedema and the symptoms in both are similar. Administration of thyroid gland brings about removal of these symptoms. It logically follows that the thyroid gland gives to the blood some secretion, which if withheld, brings about changes of mind and body characteristic of myxoedema.

In 1894, Oliver and Schafer[7] published the results of their works on the suprerenal glands showing that the extracts made from these organs possessed properties quite as wonderful as those of thyroid extract. Its action

has been found beneficial in Addison's disease, and is closely connected with the sympathetic nervous system, for if intravenously injected, it causes a great rise of blood pressure, produced by constriction of the peripheral arteries and augmentation of the heart's action. Constriction of the uterus is also produced in those animals in which the sympathetic nerve supply of that organ is motor in function.

It has now been shown that without the thyroid and suprerenal glands, life is impossible. Several observers, including Paulesco[8], have recently demonstrated that in this respect the Pituitary gland is of equal importance.

In 1895 Oliver and Schafer[2] investigated the physiological effects of an extract made from the Pituitary Body and discovered that these were not less striking than those of the more familiar extracts of thyroid and suprarenal glands.

The attempts to isolate the active principle of the pituitary secretion have, so far, given no satisfactory results, its action is very similar to that of suprarenal secretion. Both raise the blood pressure through constriction of the blood vessels, both cause contraction of the uterus. But, with regard to the pressor action, the suprarenal extract produces its effect through the sympathetic nervous system while the vaso-constriction produced by pituitary administration has no relation to this innervation, the pulmonary and coronary vessels being affected in

common with the arterioles of the system generally. While suprarenal extracted increases the rate of the pulse, pituitary extract decreases its rapidity and its action is much more prolonged. Suprarenal extract produces tonic contraction in the uterus only in those animals in which the sympathetic nerve supply to that organ is motor in function, but pituitary extract uniformly excites the uterus to tonic contractions in all species and in all conditions of functional activity. (In relation to the kidney their effects are strikingly different, for which the suprarenal extract produces constriction of the renal vessels and diminution of secretion, pituitary extract causes dilation of the vessels of the kidney, or, rather first constriction and afterwards dilation, and increased secretion).

The therapeutic value of pituitary extract can only be learned from extended clinical trials, and these, so far, as they have gone would seem to indicate that in it we possess a remedy which promises to be of great practical value no wise inferior to the better known glandular extracts.

The pituitary body consists of two lobes, developmentally and structurally quite different. The anterior lobe is the larger and is concave posteriorly for the reception of the posterior lobe which is to a great extent enveloped in it. It is developed originally as a tubular

prolongation of the ectoderm of the buccal cavity. It is made up of follicles of various shapes, composed of cubical and polygonal epithelial cells separated by connective tissue and is richly supplied with blood vessels. The posterior lobe consists of two parts, the pars intermedia and the pars nervosa. The latter is developed as a prolongation of that part of the embryonic brain which becomes the third ventricle. Its structure consists of a ground-work of ependyma and neuralgia cells and fibres containing islets of epithelial cells, many of which contain globules of colloid-like material which is also found in globular masses in tubules and vesicles extending from the pars intermedia to the infundibulum. This substance probably represents the secretion of this lobe.

The physiology of the pituitary gland is very imperfectly understood, but we know that it is necessary to life and that it supplies an internal secretion to the blood. This secretion tends to increase the contraction of the heart and blood vessels and perhaps exerts an influence on the nutrition of some of the tissues, particularly bone. It is very probable that it possesses an antitoxic action. Increased activity produces in early life gigantism and in adult life acromegaly. Diminished secretion or removal of gland is followed by great depression, apathy, mental weakness and tremors, dyspnoea, and progressive emaciation.

Diminished activity beginning in youth is characterised by signs of genital infantilism and in adult life by a tendency towards the loss of the characteristics of adolescence.

CHEMICAL COMPOSITION OF THE PITUITARY.

Schafer and Oliver[2] discovered that extracts of the whole gland produced, when injected intravenously, a great rise of blood pressure. Howell[3] showed later that the substance causing this rise was yielded only by the posterior or infundibular lobe, the anterior in this respect being inert.

In addition to nervous elements, there are islets of epithelial cells in the posterior lobe. It is probable that these cells and those of the pars intermedia are responsible for this active principle and that the nervous elements are in no wise connected with its production. It has been shown by Osborne and Vincent[9] that extracts made from ordinary tissue, whether of grey or white matter, mixed, or each separately, have no pressor or blood raising action.

The chemist has as yet been unsuccessful in discovering the chemical constitution of the active principle. Iodine has been found in the pituitary body in appreciable quantity, but it is not apparently in combination with the

pressor substance which is probably protein in nature.

The active principle is insoluble in water, alcohol and ether, but is soluble in a saline solution. It is not affected by peptic digestion, but is decomposed by prolonged tryptic digestion. It is not destroyed by boiling and it diffuses very slowly through animal membranes. The discovery establishing the possession of a similar type of activity by the pressor bases of the extract of suprarenal glands, ergot and putrid meat is of great importance, for it is probable that when the active principle of the infundibular extract is synthetised, it will be found to bear a close relationship to these in its structural formula.

Dixon and Taylor prepared extracts from placenta, which, when injected into the blood stream produced effects resembling those obtained from administration of suprarenal extract but differing in:

1st. less rapid rise of blood pressure
2nd. more prolonged rise, and
3rd. less cardiac effect.

Results, in short, very similar to those obtained by administration of pituitary extract. This preparation also causes contraction of the uterus and Dixnn and Taylor[10] believed that the active principle grew simultaneously with the placenta and was the natural stimulus for the production

of labour.

In 1909, Barger and Walpole[11] identified the pressor bases in the extract of putrid meat and found them to be the following organic amines - phenylethylamine, para-hydroxyphenylethylamine and isoamylamine. Rosenheim[12] found that the active principles of Dixon and Taylor's placental extract were identical with these amines and that a certain amount of putrefaction of the placenta is necessary for the development of this activity.

It has been shown by Barger and Dale[13] that para-hydroxyphenylethylamine which is one of the pressor bases of putrid meat, is also the chief active principle of aqueous extracts of ergot. It is very nearly related in chemical structure to the suprarenal active principle. It is of great interest to note that ergot produces its effects by acting directly on the vessels independently of the central nervous system. It is a stimulant of plain muscle. Not only in its effects but also in its modus operandi it would appear to bear more than a superficial resemblance to the active principle of pituitary extract.

Recent research has shown that there is a large number of these organic amines closely approximating in chemical structure to the suprarenal active principle and having a similarity of action to it. This knowledge satisfactorily accounts for the occurrence of a pressor action in the various fluids of organic origin.

PHARMACOLOGY OF THE PITUITARY GLAND.

It is with the posterior infundibular lobe that most investigators have concerned themselves but to state that the anterior lobe is of no functional importance is rather difficult of acceptance.[14] Falta claims that an extract of the anterior lobe lowers the blood pressure and that this effect may be counteracted by extract of the posterior lobe. There is evidence for associating disease of the anterior lobe with acromegaly and gigantism and Schiff[15] found that by giving pituitary substance to elderly men and in cases of acromegaly, there was caused an excessive loss of phosphorus, leading him to the conclusion that the gland presides over the nutrition of the osseous system. It has been suggested that this special function is confined to the anterior part of the gland. But regarding the pharmacology of the anterior lobe, practically nothing is known. It is with extracts of the posterior or infundibular lobe that the most striking results have been obtained and these manifest themselves in a slowing and strengthening of the heart beat, in a pronounced rise of blood pressure, in profuse secretion of urine and in marked tonic contractions of the uterus. The methods of administration which produce the general phenomena in characteristic rapid manner are intravenous and intramuscular injection. The active

principle diffuses slowly through animal membrane and is slowly absorbed from the stomach.

An intravenous or an intramuscular injection is followed by a great increase of the strength of the heart beat with decrease of frequency and a powerful and lasting rise of blood pressure. The greatest rise is seen about fifteen to twenty minutes after the injection and lasts for over an hour. In the following cases I took the pulse and the blood pressure by the Riva-Rocci apparatus before administration of the pituitary extract, five minutes after, fifteen minutes after, half an hour after and then hourly for four hours.

	Pulse	Blood Pressure
Before injection of 1 c.c. of Pituitrin (Park Davis & Co.)	78	110 mm.
5 minutes after injection	74	115 "
15 " " "	72	125 "
30 " " "	70	120 "
1 hour " "	66	115 "
2 " " "	66	115 "
3 " " "	66	100 "
4 " " "	68	100 "

		Pulse	Blood Pressure
II.	Before injecting 1 c.c. Pituitrin.	88	130 mm.
	5 minutes after injection	88	140 "
	15 " " "	78	150 "
	30 " " "	72	140 "
	2 hours " "	70	135 "
	3 " " "	72	130 "
	4 " " "	68	130 "
III.	Before injection of 1 c.c. of Duncan, Flookhart's extract.	84	125 "
	5 minutes after injection	80	130 "
	15 " " "	80	135 "
	30 " " "	80	130 "
	1 hour " "	74	130 "
	2 " " "	72	120 "
	3 " " "	70	120 "
	4 " " "	69	120 "
IV.	Before injection of 1 c.c. of Burroughes, Wellcome & Co's extract.	120	130 "
	5 minutes after injection	106	140 "
	15 " " "	106	150 "
	30 " " "	102	140 "
	2 hours " "	106	135 "
	3 " " "	106	130 "
	4 " " "	100	130 "

It is to be noted in these cases that the blood pressure returned to its normal condition sooner than did the pulse, and this is invariably so. I have found the pulse remain below its normal rate for more than twelve hours.

Oliver and Schafer[2] demonstrated that the increase in blood pressure is due to a constriction in the blood vessels and augmentation of the cardiac contractions and that these conditions persist after destruction of the central nervous system.

It is known that the arterioles of the lungs which receive no constrictor fibres from the sympathetic system (though it is held that the muscular walls of the pulmonary and its main branches receive motor fibres from that system), do not respond to the injection of suprarenal extract like the rest of the arterial system; with pituitary extract, on the other hand, the pulmonary arterioles are affected in common with those of the system generally.

There is not, as yet, complete agreement as to the innervation of the coronary arteries. The consensus of opinion points to their being slightly, if at all, controlled by vaso motor nerves and Dale's experiments proved that they afford another example of an arterial area stimulated to pronounced contraction by pituitary extract, while unaffected or only in a very minor degree, by suprarenal extract.

The nature of the action of pituitary extract on the heart appears to be a prolonging of systole rather than of diastole. The effect is probably due to direct action in the sarcoplasm and to the altered rate of coronary perfusion.

In 1908 Mummery and Symes[16] published the results of some experiments on the blood pressure in animals while in a state of shock and observed that when the animal is in that state pituitary extract acts much more powerfully in raising the blood pressure than in normal circumstances. During the period of action a second injection is inactive or nearly so.

Schafer and Magnus[17], and later Schafer and Herring[18] found that the injection of pituitary extract was followed by an increase in the volume of the kidneys and a prolonged and pronounced diuresis. Schafer and his co-workers attributed this diuretic action to the presence of a separate principle, also limited to the posterior lobe.

Dale[19] found that there was first a primary constriction of the vessels which was followed by a dilatation. A second injection while failing to cause any perceptible rise of blood pressure, slightly reduced the resistance of the renal vessels.

The probable explanation of the phenomenon is that the renal vessels are relatively insensitive to the vaso-

constrictor effects of the pituitary extracts. This is by no means the only instance where the renal vessels react exceptionally to general stimulants of plain muscle contraction. The drugs of the digitalis group, when injected cause swelling of the kidneys and diuresis, although their action when perfused through the isolated kidney is to cause constriction. After the injection of pituitary extract, the rise of pressure and the diminution of total capacity in the arterial system of the body generally would be sufficient to overcome the comparatively moderate amount of renal constriction and produce an actual engorgement of the kidneys and this might possibly account for the diuresis produced.

After considerable use of the different pituitary extracts on the market, I have failed to find that diuresis is an invariable result of their administration. I have observed when an injection is given in midwifery cases, there is great diuresis at the beginning of the puerperium, but then, diuresis is a normal accompaniment of the condition. In healthy young persons, the results have been negative or never pronounced. It has to be noted, however, that most observations have been made on animals in an anaesthetised condition, that is to say, in a state of shock, when it has been observed the characteristic effects of pituitary extracts are best observed. It is obvious

that the results of administration in practice do not correspond with those obtained experimentally.

ACTION ON THE UTERUS.

Suprarenal extract produces tonic contractions of the uterus only in those animals in which the sympathetic nerve supply of that organ is motor in function, but pituitary extract uniformly excites the uterus to tonic contraction in all species and in all conditions of functional activity. This latter fact was first demonstrated by Dale and later he ascertained that this action, like that on the arteries, is possessed only by the extracts of the infundibular lobe.

Cushny[20] and others have shown that in the uterus of the cat, the sympathetic nerve supply is motor in function in the pregnant condition but not so in the non-pregnant state. Suprarenal extracts stimulate the uterus of the pregnant cat, but in all other conditions, have no effect on it. Pituitary extract, on the other hand, produces tonic contractions in all functional states and so little does the effect depend on the condition of the uterus as regards oestrum or pregnancy, that Dale was able to prove that the virgin uterus of a half grown cat responded as readily to the pituitary extract as that of the pregnant animal. Intravenous injections with an animal in which the central nervous system had been destroyed, produced

equally powerful tonic contractions. The action of pituitary extract on the uterus is very similar to that of ergot. They are both stimulants of plain muscle and act independently of the central nervous system. They augment the contraction of the fibres and produce a more active peristalsis. They have an emmenagogue effect on the non-gravid uterus and an ecbolic effect in the gravid condition. The action of extracts of the posterior lobe of the pituitary on the uterus, show simply that they contain an active substance which is a powerful stimulant of plain muscle. All organs having such muscle are in varying degrees affected by this substance plus the arteries, the uterus and the spleen being observed to be those most susceptible to its action. It would appear to have no effect on voluntary muscle either directly or indirectly. It is essentially a stimulant of plain muscle.

Whilst on the subject of the pituitary gland, it may be mentioned in passing that much has been learnt recently regarding the role played by internal secretions in regulating the various functions and maintaining, by their balanced and mutually reacting stimuli, the general health of the body. There is a correlation of function. We know now that the internal secreting glands, thyroid, pituitary, thymus and suprarenal glands and probably every tissue in the body, produce chemical substances - hormones -

which by circulating in the body exercise an influence on each other and so maintain the balance and health of the individual. They act as toxins and antitoxins.

CLINICAL RESULTS.

It has already been mentioned that pituitary extract produces a rise of blood pressure and a slowing of the pulse and that it is the infundibular portion of the gland that possesses this property. In this respect it resembles other pressor substances, such as strychnine, strophanthus, digitalis and suprarenal extract, but has the marked advantage over them of producing a very much more prolonged effect. It is apparent that a substance which has the property of maintaining a raised condition of the blood pressure for several hours, must be of inestimable value in the treatment of shock, e.g. surgical shock and shock produced by excessive and rapid loss of blood during and following labour. In functional heart disease, particularly in post-influenzal cases, the administration of pituitary extract is of great value in combating the resultant symptoms.

ITS EMPLOYMENT IN UTERINE CONDITIONS.

Pituitary extract produces powerful tonic contractions of the uterus in all states of functional activity. After normal labour, I have frequently used it and always found it to produce prolonged and pronounced uterine contractions.

In this respect, its action is stronger, quicker and more persistent than that of any of the recognised preparations of ergot. In my practice, I do not usually give a uterine stimulant unless the pulse is rapid and the uterus contracting feebly. In such case, I have found that pituitary extract leaves nothing to be desired. The uterus very quickly contracts into the typical hard cricket ball form and the pulse becomes much stronger and slower. The following cases show the effect on the pulse rate.

		Pulse rate.
I.	Before injection	120
	10 minutes after injection	90
	15 " " "	72
II.	Before injection	118
	10 minutes after injection	100
	15 " " "	80
III.	Before injection	120
	10 minutes after injection	86
	15 " " "	76

		Pulse rate.
IV.	Before injection	110
	10 minutes after injection	72
	15 " " "	60
V.	Before injection	116
	10 minutes after injection	92
	15 " " "	70
VI.	Before injection	100
	10 minutes after injection	82
	15 " " "	60

It is well known that immediately after delivery, the pulse rate falls, and if this does not take place and the pulse rate remains at 100 or over, there is grave risk of post-partum haemorrhage taking place. Pituitary extract would seem to possess the property of averting this danger by firmly contracting the uterus and reducing the pulse rate to a slowness which is remarkable.

In certain cases of uterine inertia, it can readily be understood that pituitary extract must be of great service. Its value was exemplified in the following cases:

Mrs. C. 5-para. Aged 32.

On my arrival, I was told that for two hours previously, the pains had been very feeble and irregular. Her face was quite placid and did not have any indication of the characteristic expression of the usual parturient patient. On palpation, the uterus responded very feebly to manipulation. Vaginal examination showed the Os to be well dilated and the soft parts relaxed. The membranes had been ruptured for some hours. The pulse was 118 and the temperature normal.

I injected 1 c.c. of pituitrin intra-muscularly into the gluteal region and within five minutes two strong uterine contractions expelled the child.

The patient's previous confinements - especially the latter two - had been tedious and difficult instrumental cases. Her confinements had been at short intervals.

This was, obviously, a case of fatigued uterine muscle. The pituitrin stimulated its flagging energy and so hastened delivery. It can readily be understood that such a powerful ecbolic is absolutely contra-indicated unless the absence of all obstacles to rapid delivery has been ascertained. It can only be legitimate to use it for inertia when the first stage is over, the Os fully dilated and the perineum soft and yielding, although in repeated small doses, it might probably be quite safely given.

The known action of the pituitary extract on the uterine muscle at once indicates that it is likely to be of great service in uterine haemorrhages and though I have had the opportunity of trying it in two cases only of this description, the results were eminently satisfactory. The first was a case of post partum haemorrhage.

Mrs. McV. Primipara. Aged 38.

After the placenta was delivered, the pulse rate was 120, but the uterus was contracted although not very firmly. I decided to administer pituitary extract and just when I had finished preparing the injection, I observed that the patient was in great distress. I was quite unable to make out the contour of the uterus and the blood was pouring from her. I injected 1 c.c. pituitrin and massaged the uterus through the abdominal wall. The effect on the bleeding was almost instantaneous. She made a good recovery, although, as was to be expected, she was very pallid and ex-sanguine for a long time.

The other was a case of 'Accidental' Haemorrhage.

Mrs. McD. 6th pregnancy.

At end of fourth month a slight haemorrhage - a mere show - occurred. Afterwards at intervals there was a gush of blood in the morning on rising. I began treatment by injecting 10 minims of Duncan Flockhart & Co's

Pituitary Extract once daily and continued doing so for a week. Although the patient was not confined to bed, the haemorrhage ceased and a living child was born at full term.

I can remember also another case in which pituitrin served me well.

Mrs. C. 6-para. Aged 34.

On my arrival, I found she had been delivered of a full term child and I was informed by the nurse that she had lost a large quantity of blood and that she (the nurse) failed to get the placenta expressed. On observing the pallor of the patient, without waiting to make the usual preparations, I massaged the uterus through the abdominal wall and expressed the placenta without difficulty. I could not feel the radial pulse at either wrist and the pallor was extreme. The uterus was soft and very feebly contracted. She told me afterwards that she was "going blind" when I arrived. I injected c.c. pituitrin. In a few minutes the uterus contracted in the characteristic hard ball, the pulse could then be felt and it gradually increased in strength. She made a good recovery, although this was necessarily prolonged.

In the case of the post partum haemorrhage, I do not think that an ergot preparation would have been so effective for, undoubtedly, pituitary extract acts more promptly,

more surely and more strongly. In the case of 'accidental' haemorrhage, a combination of chlorodyne and ergot would probably have had an equally successful result.

It seems only natural to infer, in view of its effect upon the blood vessels and on uterine muscle that pituitary extract would be of advantage in endometritis, leucorrhoea and menorrhagia. In all those conditions I have used it with beneficial results.

A case of endometritis. Mrs. McL. Aged 30.

The uterus was enlarged. Menorrhagia was present, the menstrual flow lasting at each period for about 10 days. The other symptoms were dysmenorrhoea, a rusty-tinged leucorrhoeal discharge, pain in the back, anaemia and great depression of spirits. When first called to see her, she had been menstruating for four days. I gave her 1 c.c. Parke, Davis & Co's pituitrin intramuscularly, which was followed almost immediately by a sharp cutting pain in the uterus, the result, undoubtedly, of the contraction of the inflamed organ. On the following day I administered a similar dose and within twelve hours, the menstrual discharge had entirely ceased, after having lasted only a little over five days instead of ten as was commonly the case with her. Every second day thereafter I injected ½ c.c. of pituitrin until the next menstrual period when there was less dysmenorrhoea and although I gave no

injection while it lasted, the flow ceased in five days. I continued the same treatment until the next menstrual period which lasted barely five days and she was entirely free from pain.

The patient had no douches or tonics. The treatment consisted entirely of ½c.c. pituitrin every second day for three months, Epsom salts every second morning and regular exercise. Six months after beginning of treatment, the patient was enjoying normal good health, the endometritis being apparently quite cured.

A case of Menorrhagia. Miss MacI. aged 29.

Had lost a large quantity since onset of menstruation at 15.

When I first saw her (March 1912) she had profuse loss with clots passing at each period which lasted about nine days each period. The other symptoms were dysmenorrhoea, pain in back, anaemia, indigestion and lethargy.

The uterus was enlarged and tender.

As the flow was ceasing at my first visit, I first of all treated her for dyspepsia and with a view to improving her appetite. At commencement of following period, I gave her gr.2 tabloids pituitary gland (Burroughs, Wellcome & Co's) internally, beginning with one twice daily and increasing the dose until she took four daily. This was continued for twelve weeks. At the end of this time,

I discontinued the tabloids as I found no appreciable improvement in her condition. I intend, when it suits the patient's convenience, to try the injections of pituitrin as I did in the first case.

In leucorrhoea I have had good results. The vaso-constrictor effect on the mucous membrane of the uterus and the striking tonic effects on the uterine muscle of pituitary extract when administered intra-muscularly, sufficiently explain, I think, the success of the treatment in these cases.

So far I have demonstrated in my practice that pituitary extract has been a very useful remedy for various pathological conditions of the uterus. I have tried to select cases in which good results might be expected, taking as my guide the physiological action of the drug so far as it is known and the experience of others. In most of my trials I met with more or less success, but in others I was unsuccessful.

DOSAGE AND METHOD OF USING.

The preparations I have used are Parke, Davis & Co's Pituitrin, Duncan Flockhart & Co's Pituitary Fluid and Burroughs Wellcome & Co's Pituitary Extract and Tabloids.

To secure rapidity of action, the best and most convenient method of administration is by intramuscular injection, either into the deltoid region, into the supinator group or into the gluteal region. When given by the mouth it is but slowly absorbed and, in my experience, the results are very doubtful. I have given pituitary gland tabloids internally in cases of exophthalmic goitre with but very indifferent results whereas the same cases responded quickly to intramuscular injections of pituitary extract.

In very urgent cases of shock or uterine haemorrhage, it should be given intravenously and it has to be kept in mind that a second dose, if necessary, will not produce more than a fraction of its proper effect unless some time has elapsed since the previous dose was given.

The dose ranges from 0.5 c.c. to 1 c.c. hypodermically and up to 1.5 c.c. by the mouth. The patient should be carefully watched and the arterial pressure taken as a guide to the necessity of modifying the dose given.

The difficulty of interpreting the results of the administration of pituitary extract is very great. A better knowledge of the functions of the gland and the discovery of the chemical composition of its active principle would be of inestimable value in the solution of the problem. Experiments and clinical trials have

revealed to us that the extract is a highly active substance but much work remains to be done before its full therapeutic value can be appreciated. But, incomplete though our knowledge at present is, the results so far are sufficiently conclusive to warrant the belief that in it we have a remedy which will be of great benefit to mankind.

SUMMARY AND CONCLUSIONS.

While the majority of observers have come to the conclusion that extracts of the anterior lobe of the pituitary body are inactive, clinical and experimental work have shown that extracts of the infundibular or posterior lobe possess very active properties.

Infundibular extract produces a marked rise of blood pressure, it lessens the pulse rate and augments its energy. The rise is prolonged, lasting for over an hour and reaching its maximum about fifteen or twenty minutes after its administration. The decrease in the pulse rate lasts much longer - for twelve hours or even longer. Irregular heart action becomes more regular.

The action of the extract on the uterus is to produce powerful tonic contraction on the organ. Its action in this respect is more rapid and persistent than that of ergot preparations.

In my practice, over a widely distributed country area, I have frequently arrived at a labour case to find that the birth has taken place with or without expulsion of the placenta. Sometimes I have found, in such cases, the patient in a state of collapse from loss of blood, of pale colour, and as they express it afterwards "going blind" pulse, either cannot be felt or very feebly so and rapid. On palpation, the uterus is found to be soft and uncontracted and responding feebly to massage. In such cases, I have found the injection into the gluteal or deltoid muscle followed quickly by contraction of the uterus into the hard cricket ball form, cessation of haemorrhage, pulse becomes slower and stronger and the patient gradually regains full consciousness.

In cases of exhaustion with uterine inertia following on prolonged labour, as seen in poor, under-fed women of the working class, and where confinements have taken place at short intervals, where there is no obstacle to rapid delivery, the injection intramuscularly of pituitary extract brings about uterine activity and a speedy termination of labour. In such cases, I have found the use of pituitary extract of great service, second in importance only to its value where the uterus fails to contract after delivery and there is threatened or actual post partum haemorrhage.

After normal labour, it is of value as a prophylactic against haemorrhage and after pains.

In haemorrhage it is beneficial by its vaso-constrictor action and its tonic effect on the uterine mucous membrane.

In leucorrhoea I have found pituitary extract useful, but it is difficult to say how much of the credit is due to it owing to use at the same time of local remedies, such as douches, medicinal (tonic) treatment and attention to hygienic conditions.

There is, no doubt, much difficulty in interpreting the results, the whole matter being, as yet, in an experimental stage, but the success already achieved, gives promise that in pituitary extract we have a remedy which, if judicially used, will finally be of great help to the obstetrician.

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