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THE PITUITARY AND THE PHARMACOLOGICAL ACTION
OF ITS EXTRACT.

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by

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I N T R O D U C T I O N .

Until recently the group of glands now called the endocrine glands was not recognised, they being regarded as mere vestigial organs of no function. Only during the latter half of last century attention was directed to them by various changes noted in them after disease, and by changes noted, when they were diseased or removed, partly or entirely. Theories were then held that they poured out a secretion into the blood.

Before this it was the common view that the pituitary poured out a secretion as described by Galen, which produced phlegm or pituita, which was discharged through the nose. Though this was the theory held, the fact must not be lost sight of that as early as 1672 Richard Lower wrote an inspiring treatise to the effect that: "For whatever serum is separated into the ventricles of the brain and issues out of them through the infundibulum to the glandula pituitaria distils not upon the palate but is poured again into the blood and is mixed with it". (Bell)

After the discovery that certain glands had an internal secretion it was noted that some, such as the/

the pancreas, testes, etc. had both an internal and an external secretion.

Later, knowledge of these internal secretory organs was increased by noting the effect when extracts of them were injected into the system. Nevertheless, although it was realized that there existed a very close relationship between these organs, constituting the hormonopoietic system, comparatively little was known about this relationship. Even at present the various views held on the subject are very conflicting. Although synthetic preparations have been made having the same properties as the natural extract of some of these glands, very little is known of the chemistry of their secretions. Of these much neglected organs, the pituitary which I have chosen to discuss has suffered greatest inattention, partly perhaps owing to its position of difficult access, and partly because its pressor action is so closely resembled by that of the suprarenal secretion, which received fairly full attention after 1855 when Addison described the effect of destruction of the suprarenals, and after Oliver and Schäfer discovered the extract. Though the administration of this extract did not cause any improvement in disease, its other actions of causing local contraction/

contraction of blood vessels, its cardiac stimulant effect, its effect of causing uterine contraction, etc., brought it into prominence.

The thyroid received first attention in 1859 when Schiff extirpated the gland from animals which subsequently died unless supplied with a piece of subcutaneously grafted thyroid. He later showed the occurrence of marked improvement after administering the extract to cases suffering from lack of thyroid secretion, such as cretins, myxoedematous persons and certain cases of exophthalmos.

So also did the other ductless glands receive attention with the discovery of their internal secretory functions, their relationship however, being understood only in so far as it was noted that diminished or increased action of any one of them, effected changes in others of the group.

Our knowledge of the subject of the endocrine system is still but vague, and it may yet be discovered that internal secretory functions exist in organs which to our present knowledge possess only other functions. In this thesis I propose to confine myself in main to the pituitary, its functions and the uses to which its extracts have been put, and also to embody an account of my own small experiences in the employment of the drug.

H I S T O R I C A L.

The earliest scientific investigations of the pituitary, date from 1838, when Rathke described the hypophysis as originating from the primitive alimentary canal. He thought the hypophysial pouch was entodermal in origin. Later, however, Balfour showed it to be of ectodermal origin. Although comparatively great research work on this organ was subsequently undertaken, and extracts of the gland made, the nature of the active principle of pituitrin is still unknown. Abel and Kubota state that histamine is an important active principle whereas Jackson and Mills say that although histamine is present in the gland and tissues, the active principle is a simple body which they call of the sympathomimetic-amine type (Med. Annual, 1921).

Oliver and Schäfer noted that the extract caused a rise in the blood pressure with a vasoconstriction, after being introduced into the system.

In 1904, Herring described the action of the extract more fully, though to Bell and Hick belong the credit of first describing its action on the uterine muscle.

Dale then showed that the entire action was upon unstriated/

unstripped muscle, thus differing from suprarenal extract which acts through the sympathetic nervous system.

It is interesting to note that Jackson and Mills ascribe its action as being on the nervous and not the muscular element (Med. Annual, 1921).

In 1909 Blair Bell brought pituitary into prominent notice, describing its action in shock and also its action on unstripped muscles such as the uterus and intestines.

The earliest recorded experiments on human beings date from 1896 when Mairet and Bosc, by injecting extract of the pituitary gland of an ox into the human system produced increased pulse-rate, increased urinary excretion and increased urea, lasting 24 hours.

The following year, however, Schiff stated that there occurred no increase in the urine.

Parisot, several years later, recorded the facts noted at the present day. He stated in 1907 that there occurred no qualitative alterations in the urinary excretion, that the pulse rate was slowed, and the blood pressure raised, while the urine was increased in quantity.

In 1906-7, Delille stated that extracts of the anterior lobe produced none of these effects, though the slowed pulse, raised blood pressure, and diuresis occurred/

occurred from the entire gland extract, and much more so, from the extract of the posterior lobe.

Lewis and Miller described an inhibitory substance - depressor substance - soluble in alcohol, present in the gland, which they said interfered with the pressor substance, present in the pars intermedia only.

Dale mentions that this pressor substance passes into the urine.

It is possibly this pressor substance which causes the rise in blood pressure noted during labour, and which falls gradually after labour, although Dixon and Taylor ascribe this rise to an internal secretion of the placenta, while Rosenheim puts it down to a pressor substance produced during incipient putrification of the placenta (Cushing).

Such a substance however does form when meat putrifies.

Rather vague knowledge was added later, by the experiments of Paulesco and Cushing that an animal died more quickly after removal of the anterior than of the posterior parts of the gland. They discovered later that with an increased activity? or administration of the posterior gland substance, the carbohydrate tolerance was diminished, with a possible glycosuria; and also when, through disease, there occurred a diminished secretion, the carbohydrate tolerance/

tolerance increased. (Howell) With all these additional findings in the nature and behaviour of the gland, one is still in the dark as to how the secretion enters the system and as to the exact behaviour of the gland in the normal healthy individual.

Much that is lacking, however, sufficient is known about the pituitary to supply a great proportion of the long-felt want in the treatment of a number of conditions.

Fig. 1.

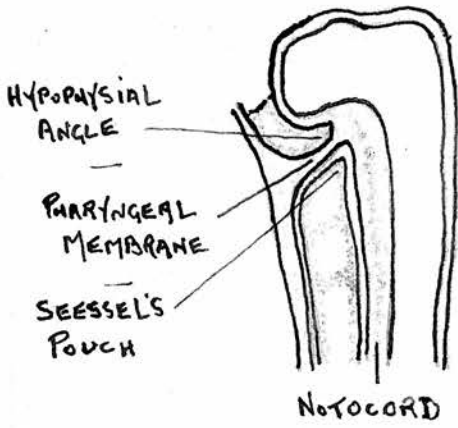


Fig. 2.

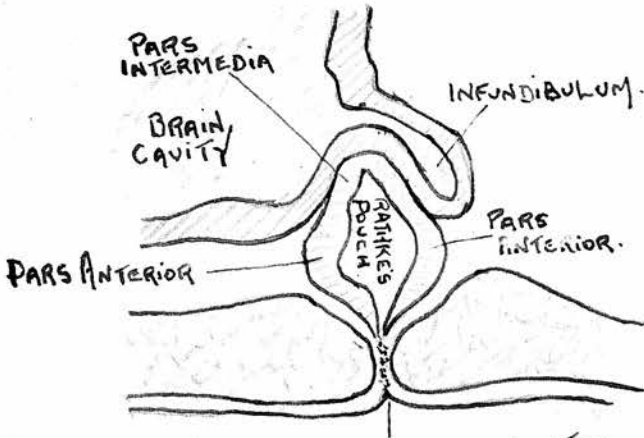
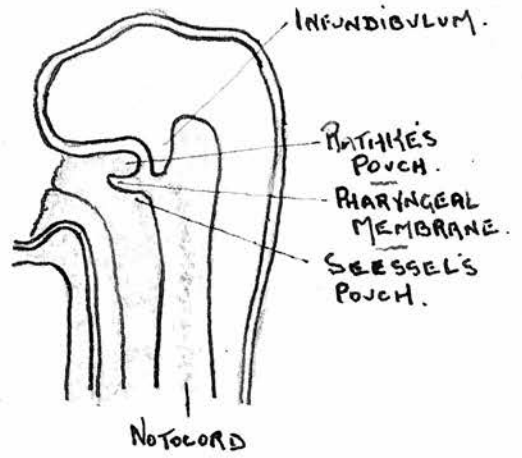


Fig. 3.

COLUMN OF CELLS IN THE SPHENOID BONE, MARKING THE NECK OF RATHKE'S POUCH.

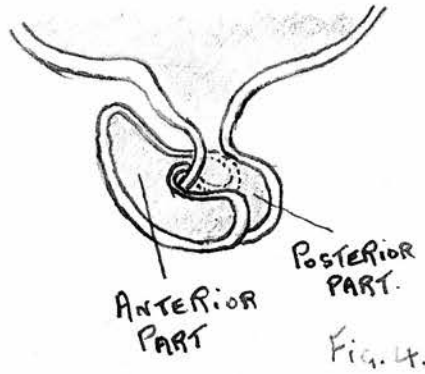


Fig. 4.

FROM BELL'S: "THE PITUITARY"

D E V E L O P M E N T .

The first sign of the hypophysis exists as the hypophysis angle, later called Rathke's pouch, lying between the pharyngeal membrane and the roof of the primary stomodeum. The membrane breaks down and Rathke's pouch becomes larger and deeper in front of it. Behind it, at the highest part of the roof of the stomodeum, another pouch forms, known as the pouch of Seessel. (See diagrams)

The former pouch is ectodermal in origin, the latter entodermal. Their posterior parts are limited by the notocord, which - in man - plays no part in the formation of the pituitary.

As the pouch of Rathke deepens and the stump of the pharyngeal membrane bends forwards, a portion of the floor of the embryonic brain is dragged down to form a hollow process behind it.

Nextly the pouch of Rathke develops a constricted portion which is ultimately obliterated by the formation of the sphenoidal cartilage.

The descending infundibulum from the brain now comes into closer relationship with the hypophysis, continuing/

continuing its downgrowth past the posterior portion, whose lateral processes partly envelope it.

Owing to its mode of origin, the hollow anterior portion shows a glandular structure, which ultimately becomes more compressed, showing the remains of the pouch as a cleft.

The part lying posterior to this central cavity remains in close contact with the neck and sides of the infundibulum and goes to form the pars intermedia.

At this stage, the infundibulum, which contains a cavity continuous with that of the third ventricle, becomes differentiated, by its lower portion showing no signs of being hollow. The upper portion or stem is now known as the infundibulum, while its lower or neuroglial portion becomes the posterior or rather, nervous portion of the pituitary.

A N A T O M Y.

Quain's Anatomy: Cunningham's Anatomy
and Bell's Pituitary.

The pituitary consists as has been shown, of an anterior and a posterior part.

On section the anterior part is soft and pinkish or yellowish in appearance, while the posterior lobe is white and paste-like.

In/

In mammals, the anterior part is larger than the posterior, fitting on the posterior part like a cap, and separated from it by a cleft, immediately behind which is situated the pars intermedia.

The entire gland weighs about .56 grammes (Bell), .46 (Halliburton).

It generally increases in size and weight during pregnancy and decreases in old age. Sex differences are said to exist. Average dimensions:- 14.4 mm. in transverse diameter, 11.5 mm. antero-posteriorly and 5.5 mm. vertically.

The entire gland lies in the pituitary fossa in the cranial fossa. Its relationship to the sphenoidal sinuses varies even in normal individuals, lying sometimes above, and sometimes behind it.

The sella turcica is lined by a layer of dura mater which stretches from the four clinoid processes to form a cover for the gland, leaving a small aperture for the stalk by which the gland is attached to the tuber cinereum.

It is surrounded by a plexus of veins radiating outwards from it. These veins unite with the cavernous sinuses on its sides, with the anterior communicating sinus in front and the posterior communicating sinus at the back.

Round about it also lies the circle of Willis, with the anterior communicating artery joining the anterior/

anterior cerebrals in front, the internal carotids and posterior communicating on its sides, and the posterior cerebrals behind.

Slightly above and anteriorly, the optic chiasma lies in close relationship to it, while behind it lie the two mamillary bodies. Somewhat further from it lie the oculo-motor nerves, passing forwards and outwards along its sides.

HISTOLOGICAL ANATOMY.

The pars anterior: consists of epithelial cells supported by connective tissue, separated by blood vessels and sinuses, and lined by a single layer of endothelium.

The cells are eosinophil, basophil or neutrophil, the eosinophils having a centrally placed nucleus, while the nucleus of the basophil generally lies at the periphery.

Eosinophil cells are often arranged in an acinous form, and have a granular secretion. They stain with acid dyes, thus differing from the basophil cells which have a more homogenous secretion of colloid, and stain basic.

Sympathetic nerve fibres pass into the gland substance/

substance at right angles to its surface, crossing the sinuses and ending, after dividing amongst the intercellular tissues, in small ball-like terminations.

The pars intermedia: consists also of a glandular structure with neutrophil and basophil cells. It secretes, especially in pregnancy and advanced age a colloid material. Blood vessels are absent and intercellular tissue but scanty (Bell). According to Quain's anatomy, blood-vessels exist, though not so plentifully as in the pars anterior. Its cells, at the edge of the cleft, are somewhat flattened, and triangular, one angle dipping into the tissues.

The pars nervosa: consists mainly of neuroglial cells and fibres. True nerve cells are said to be absent.

A pigment of unknown nature also exists in this part.

HISTOLOGICAL OBSERVATIONS.

Pars Anterior: In pregnancy the enlarged anterior lobe shows a change, with an increase in the eosinophil cells and also of the granular material. Colloid material also is more abundant. It is derived, according to Bell, from the eosinophil cells, whose granular secretion has not been discharged into the blood/

blood sinuses and has undergone a subsequent chemical alteration, becoming more homogeneous and adopting a different staining property.

A shrinking of the epithelial cells occurs in certain physiological conditions in animals and birds, such as hibernation and brooding and according to Bell, also in man, in physiological sleep. The nuclei show up more distinctly and there is a lessened secretory activity.

In disease of the anterior lobe, causing a lessened secretion, there is often drowsiness and a deposit of subcutaneous fat.

Each type of cell is said to have a function of its own. Blair Bell however says that neutrophil, eosinophil and basophil cells are the same in different phases of secretory activity.

Pars Intermedia: Instead of neutrophil cells, eosinophil cells may abound, though the secretion generally found in the cleft, is usually colloid and not granular.

Pars Nervosa: Sometimes portions of the pars intermedia project into this part, so that colloid material may occur in the pars nervosa.

As the pars intermedia has no blood-vessels, it discharges its secretion into the pars nervosa and thence/

thence into the third ventricle (Cushing) or into the blood stream (Bell).

Some authorities believe the pressor substance to be derived from the pars nervosa. The majority however state that it is derived from the pars intermedia, from where it passes into the pars nervosa.

John Fraser claims that definite changes occur in the gland, especially the cleft and pars intermedia, in children, in whom the remains of the pouch is dilated and contains a granular and colloid secretion. This secretion, he states, is derived from the pars intermedia and pars anterior, and is deposited temporarily in the pituitary lake, as the blood vessels of the glands are unable to cope with it.

CHEMISTRY OF THE PITUITARY EXTRACT.

Except for a few facts, also disputed by many, but little is known of the chemistry of the pituitary extract.

The colloid from the anterior lobe is insoluble in alcohol and ether.

The secretion from the posterior part is not a protein, being soluble in water but not destroyed by heat.

Not knowing its chemical nature one is unable to/

to say with certainty whether or not it is present in the cerebro-spinal fluid as asserted by a number of writers, or for that matter, in any other parts of the body.

INJECTION RESULTS.

Circulatory System: It differs in its effect upon the circulatory system from supra-renal extract in not being so marked, though more prolonged than the latter.

The active extract, derived from the posterior lobe causes a slowing of the pulse with an increase in the blood pressure, the heart action being increased in force. This effect is not altered by section of the vagus, thus showing its peripheral action.

Subsequent injections of infundibulin given soon after, produce little or no effect on the circulatory system, until the first effect has passed off (Howell).

The arteries of the lungs and coronary arteries, whose muscular coats are not controlled by the sympathetic nerves, are not contracted by the supra-renal extract, but are by pituitary extract.

Spleen/

Spleen: This organ is said to be slightly contracted by pituitary extract.

Dazzi states that injection of adrenalin causes appearance of haemamoebæ in the blood in latent malaria, ascribing this to contraction of the spleen. It would be interesting to know whether the same result follows an injection of pituitary extract. It would also be interesting to know whether the lack in the rise of blood-pressure noted in cases of dementia præcox after injection of adrenalin is noticeable after an injection of pituitrin. (Med. Annual 1921)

Respiratory System: The only effect upon respiration, is a diminution in the amplitude of respiratory movements.

Urinary System: The kidneys produce an increased secretion not due entirely to the dilatation of its blood vessels which follows an injection of infundibulin.

The bladder is said to contract as a result of injection of pituitary.

Bell says bladder contraction occurs only as a result of extreme dilatation of the organ.

Uterus: The pregnant uterus contracts very markedly after injection of the extract. Ergotin, which negatives the action of adrenalin subsequently given, does not prevent the contraction resulting from pituitrin.

Some authorities deny the property of infundibulin to contract the non-pregnant uterus.

Intestines: Contractions and peristalsis of the intestines occur after injections of infundibular extract.

As in the case of all unstriated muscle, contraction is much more marked when there exists an atony of the muscle. The tone of the stomach is said to be increased, and according to Houssay, the gastric juice is also increased.

Mamma: It is said that the immediate effect of pituitary extract, is to cause an increased flow of milk. This, however, is temporary, being followed by a decrease, so that the total amount is not increased. Actual milk secretion cannot be induced with infundibulin, the noted increase being due merely to contraction of the muscle fibres of the mamma.

Pancreas: The secretion of the pancreas is said to be diminished, even after stimulation with hydrochloric acid, thus again demonstrating its peripheral action.

Eye: Pituitrin causes a dilatation of the pupils, probably by acting peripherally upon the sympathetic supplied dilator pupillary muscle.

EFFECTS OF REMOVAL OF THE GLAND.

Anterior lobe: Removal of the entire anterior lobe is said to lead invariably to death, though Handelsman and Horseley are said to have removed this portion in animals which subsequently survived. Possibly, they removed only part of the gland, as it is known that large portions may be removed, without any greater ill-effects than a somewhat stunted growth - in the young - and an increased deposit of subcutaneous fat (Cushing). Blair Bell denies this, admitting that the uterus and ovaries become atrophied.

Posterior lobe: Removal of the entire, or part of this lobe may be effected with no resultant change in development or in the uterus or ovaries.

The carbohydrate tolerance is said to be increased, permitting of large quantities of sugar to be ingested without a resulting glycosuria.

Infundibulin increases the power of changing sugar into fat (Howell).

Anterior and posterior lobes: may be partially removed, without any apparent ill after-effects, as may be noted in the case of a bitch in which Bell removed part of the anterior and posterior lobes, and which subsequently not alone improved in weight but came on heat and had coitus, not however resulting in pregnancy.

INTER-RELATIONSHIP WITH REST OF HORMONOPOIETIC SYSTEM.

Removal of the thyroid and castration, cause an increased function in the pituitary. The interpretations of this are rather conflicting. Some authorities state that the pituitary acts as a supplementary organ supplying the deficient secretion of the thyroid and gonads. Others hold that these glands have an inhibitory action on the pituitary secretion.

Hyperpituitarism causes a deficient thyroid secretion, while hypopituitarism gives rise to an increased secretion of thyroid (Cushing) Bell however definitely states that he finds beneficial results from administering infundibular extract in cases of hyperthyroidism.

P A T H O L O G Y.

Acromegaly: is caused by a hypersecretion of the epithelial portion of the pituitary, coming on after the epiphysis has united to the diaphysis in skeletal bones. It shows itself as an increase in size of the malar and lower jaw bones, with a resultant separation of the teeth. The hands and feet enlarge, and become spade-like, owing to an increased deposit of bone, and, at the same time, an arrest in bone absorption, /

absorption, which goes on in normal cases. There occurs a characteristic "tufting" of the distal phalanges.

There occurs in women, a kind of reverting towards masculinity with amenorrhoea and sterility.

In men, impotence follows a short preliminary increased sexual virility.

In both, the skin becomes thick and dry, and the nose, ears and tongue enlarge. Later, pressure symptoms may appear in the eyes.

A noted feature is the increased retention of calcium and magnesium salts.

Gigantism: is an analogous condition in the growing individual, i.e., when the epiphyses have not yet united.

In females, the tendency towards masculinity is noted in the gruff voice, and an overgrowth of the clitoris.

In males there may occur sexual precocity.

In both there is a greatly increased growth.

The hypophysis shows an increase in the number of eosinophil cells.

Disease however may exist in the anterior lobe with no accompanying symptoms, while symptoms may exist, without any change being noted in the gland. Such cases may find explanation in their resembling the case quoted by Bell, where alterations were found in/

in a part included in the sphenoidal bone below the sella turcica.

Adiposa genitalis dystrophia: is an opposite condition of decreased hypophyseal secretion, characterised by a tendency towards feminine peculiarities.

In the female, amenorrhoea results, while in the male there occurs atrophy, or undevelopment of the genitals, with increased size of the breasts and a high-pitched voice.

In both a great deposit of subcutaneous flabby fat occurs, with a diminution in the body temperature.

The carbohydrate tolerance is increased, permitting of large quantities of sugar to be taken without any resulting glycosuria.

In youth there is frequently a stunting of the growth.

This seems to indicate that the anterior lobe secretion controls growth and explains why, in the growing period, mentioned by Fraser, there occurs an eosinophil increase in this lobe, during this period.

The lowered body temperature is however not raised by injection of anterior lobe extract, but is, as shown by Cushing, with extract of the posterior lobe. Cushing calls this the "thermic reaction".

Pathological conditions of the various endocrine glands shows that they are definitely related to the pituitary; /

pituitary; for example disease of the testes and ovaries causes changes in the hypophysis, whereas disease of the pituitary, as has been stated, causes atrophy of the gonads.

Insufficiency of secretory activity of the gonads is said to lead to a hyperpituitarism with increased eosinophils. This leads one to wonder whether the pituitary activity, said to occur in pregnancy, is not a compensatory, or associated activity, brought on by inactivity of the ovarian internal secretion.

If this be so, it seems probable that it is this pituitary hypersecretion that causes the constant though small uterine contractions occurring during pregnancy. Possibly a point of saturation is reached - if one might so term it - sufficient to bring on the stronger contractions of uterus which cause labour. That it may partially be a causal factor in determining the onset of labour is merely a suggestion not based on any experimental findings.

If not out of place, one might also speculate here on the possibility of this hyperactivity of the pituitary, as being an associated causal factor of abortions so common in severe infections.

Bell states definitely that an increased pituitary secretion occurs in severe infections. In fact he supports the view that certain long-continued infections, such as typhoid fever, may actually be an etiological factor in the occurrence of/
of/

of some cases of acromegaly, and Cushing believes that a hypohypophysism means a lowered resistance to infections.

It seems likely that this increased activity in severe infection is sufficient to sensitize the uterus sufficiently to permit it to react to other stimuli, such as congestion, and so assist in the abortion which so frequently follows.

Rather difficult to interpret, is the association between the suprarenals and the pituitary. Bell quotes a case of hyperhypophysism with an increased suprarenal activity showing both characteristic acromegaly and Addison's disease, while Cushing mentions the relationship between hypersuprarenalism and hypopituitarism as often being close.

Removal of the thyroid causes various changes to occur in the pituitary, and disease of the pituitary is said (Furnival) to produce changes in the thyroid.

In cretinism and myxoedema the pars anterior and pars intermedia are said to show an increase in the chromophobe cells, and in exophthalmic goitre basophil cells predominate in these parts.

Bell believes that there exists a close relationship between the pituitary and the pineal glands.

T H E R A P E U T I C S .

The active principle of the gland is soluble in saline solution and is, in its preparation, dissolved out in this way from the dried, powdered gland. It is not destroyed by heat and can thus be readily sterilized.

It is not affected by pepsin digestion, but is destroyed by trypsin digestion, so that when administered orally, its effect is greatly nullified by the pancreatic secretion. Schäfer and Herring state that pepsin, while impairing its pressor effect, does not affect its diuretic action.

As previously mentioned, it causes a rapid rise in blood-pressure, a slowing of the pulse rate and also an increased force of heart beat.

Its action is a peripheral one on unstriated muscle, causing contractions of the uterus, intestines, bladder, etc. and of arteries, except in the kidney vessels, which it frequently dilates.

Second injections, given soon after the first, cause continued uterine contraction and diuresis, but have ~~an~~ increased effect on the blood-pressure.

The effect upon unstriated muscle, is greater when a state of atony exists, than when the muscle is normal.

The/

The posterior lobe extract is generally used, the therapeutic uses of the anterior lobe extract, not being so well defined. Its use is contraindicated:

- (a) in signs of respiratory failure during operations.
It must herebe noted that Major C.A.F. Kingston, Professor of Midwifery, Medical College, Madras, claims that it stimulates the respiratory centre (p.8 of his article).
- (b) in cases of uncompensated heart lesions.
- (c) in cases with high arterial tension.
- (d) shortly after suture-operations on the intestines.
- (e) in labour, with marked disproportion in the size of the foetal head and maternal pelvis.
- (f) in obstructed labours, or in malpresentation of the foetus such as persistent mento-posterior.
- (g) in cases where the entire lower uterine segment is not "taken up" by the advancing part of the foetus.

U S E S.

Its greatest therapeutic value may be noted in its uses on the circulatory and urinary systems, the uterus and alimentary tract.

Shock: without great loss of blood is wonderfully well overcome by the use of this drug alone. Also with marked loss of blood, it has great beneficial value/

value when a preliminary saline infusion is performed.

Sepsis: often causes a lowered blood pressure with atony of involuntary muscles, and these are markedly improved by pituitary extract.

Labour: is greatly hastened by this extract. Contractions are not alone accentuated by infundibulin, but the uterine muscles are actually sensitized - according to Bell - to react more readily to such stimuli as dilatation of the cervix or introduction of bougies, or even gentle manual kneading.

According to him a pressor substance exists in the blood which sensitizes the uterus to mechanical stimulation. What this substance may be, he makes no attempt to explain. Possibly, it is pituitary extract itself. Lack of this substance may be a partial cause of primary uterine inertia, a condition which is effectively and rapidly overcome by intramuscular injection of infundibulin. Secondary uterine inertia, after rest and proper attention is also overcome by such injections.

Placenta praevia, is another condition in which it may be used with great advantage, after rupture of the membranes, turning of the foetus, etc.

Post Partum Haemorrhage is effectively checked in many instances, with pituitrin, especially when a preliminary "sensitizing" dose be given - if one might/

might so term it - of pituitrin, followed by another dose of pituitrin or of ergotin.

Caesarian section is much assisted by the effective uterine contraction and lessened bleeding when pituitrin be given during the operation.

Expulsion of the ovum in the first half of the gestation period cannot according to Bell, take place, the uterus merely closing down upon the embryo, when the drug is administered.

My case quoted, does not seem to bear this out.

In osteomalacia: there is a deficient calcium retention. Bell advocates the use of calcium lactate gr. V. t.i.d and dried posterior gland of pituitary gr. V, and claims good results from this.

Anaesthetics, and such narcotics as morphia, scopolamine, etc. have very little reducing effect upon the uterine contractions induced by infundibulin, and are advantageously combined with it.

Care must however be taken as cases may occur, in which the child is cyanosed and has a slowed heart action, after violent uterine contractions.

Menorrhagia and uterine bleeding are often controlled by pituitrin.

In loss of tone of the intestinal muscles, e.g. post operative, great improvement may follow the use of pituitrin.

Infundibulin is frequently successful in producing/

producing diuresis in cases of anuria.

Contraction of the bladder when not functioning, ^{is} ~~are~~ said to be stimulated by the use of infundibulin, though this is denied by Bell.

Bad effects: have been known to occur when it is used in cases in which it is contraindicated, such as, before full dilatation of the os, though Madill and Allen at the Rotunda Hospital, Dublin, have given it in cases where the os is only $\frac{1}{4}$ dilated, with excellent results.

Haemorrhage may occur if the placenta be not expressed within 20 minutes of the injection of the extract.

CLINICAL WORK.

Before attempting to make practically a routine use of the drug in Midwifery I made a series of observations on the blood pressure in labour and during the puerperium.

In the comparatively few cases I found as a rule that the pressure was high during labour, falling gradually afterwards, the pulse rate dropping *pari passu*, owing to the relatively high blood pressure. I felt somewhat anxious as to the result of injecting so powerful a pressor substance as pituitrin. I however adopted its use in nearly all my confinement cases, and append a report of some of these, together with others I had permission to make observations on, in hospital, as also non-obstetric cases which I experienced in private practice.

Cases closely resembling each other are not all mentioned, conclusions being drawn however from these also.

I have used preparations of P. D. & Co., and of B. W. & Co. The former supplies phials of .5 cc. containing .2 gramme of the gland extract while 1 cc. of B. W. & Co. also contain .2 gramme.

CASE I./

CASE I. Patient, male, aet. 29.

Had been in conflict with natives. When I saw him his right shoulder was "out of joint" and he was suffering markedly from shock.

Pulse 100. Blood pressure 100.

He immediately got a hypodermic injection of morphia gr. $\frac{1}{4}$ and 1 cc. of pituitrin intramuscularly.

The dislocation was then reduced. In 20 minutes his pulse fell to 66 and his blood pressure went up to 120.

CASE II. Patient, male, aet. 32.

Had his hand severely crushed between the buffers of two railway carriages.

When seen, his blood pressure was 100, and his pulse 116.

Ten minutes after receiving 1 cc. of pituitrin intramuscularly the blood pressure rose to 120.

Two hours later he was brought to my surgery where the hand was dressed under chloroform. Half an hour later he again collapsed, with a blood pressure of 100 and a pulse of 100. Another 1 cc. of pituitrin was given, followed in about 5 minutes by a maintained pulse of 70 and blood pressure of 120, and also a diuresis.

CASE III. Patient, male, aet. 16.

When seen, he presented a marked ashen colour with a blood pressure of 85 and a very thready pulse of 118.

History was that he had been "ordered by his father to finish a cigar he had been caught smoking" He was later found in a dead faint, and smelling salts had little effect in bringing him round.

1 cc. of pituitrin was followed by violent vomiting and headache, but in 5 minutes, a fall of the pulse-rate to 76, and a rise of the blood pressure to 120. He had a desire to micturate, and promptly did so.

With the assistance of a purgative he was perfectly normal the following day.

CASE IV. Patient, male, aet. 35.

Had a fractured femur after a motor accident.

I saw him nearly 24 hours after the accident when his blood pressure was 110 and his pulse 88. For some time before I saw him he had had frequent doses of brandy and for some unknown reason, an injection of digitalis, by a nurse who was on the spot. .5 cc. of pituitrin (P. D. & Co.) was followed/

followed in 20 minutes by extraordinary improvement. The pulse had dropped to 68 and the blood pressure had risen to 130. He also had a notable diuresis.

CASE V. Male, aet. 27.

Patient had had an operation in hospital for a gangrenous appendicitis, and informed me that he had 7" of his bowel removed. Since then, nearly 8 months previous to my seeing him, he had suffered from severe constipation.

I gave him intramuscular injections of pituitrin .5 cc. (B. W. & Co.) every morning and 5 grs. of pituitrin tablets t.i.d. and also liquid paraffin. He complained of frequent desire to micturate.

The liquid paraffin and the injections were stopped after 5 days, and the tablets continued for 2½ weeks, after which his bowels moved regularly without the assistance of an aperient. Six months later he informed me he "had not yet used a purgative".

CASE VI. Patient, female, aet. 27.

Had an exophthalmic goitre with a rapid pulse of 90. Her blood pressure was only 125. Exophthalmos not very marked. Fine tremors of the fingers.

Most/

Most of the other signs were absent except that the enlarged thyroid could be made out. She had a flushing of the skin and had fits of weeping and laughing, with no obvious cause for these.

.5 cc. of pituitrin (B. W. & Co.) gave her severe headache but reduced her pulse to 80.

I gave her 5 grs. of pituitary extract tablets t.i.d. and she stated 8 days later that she had never experienced such an improvement with any drug she had taken.

CASE VII. Patient, female, aet. 41.

Had severe asthma lasting for about 7 years. Her normal temperature was 96⁰ F.

Having failed to ascertain any cause for the attacks, I gave her .5 cc. pituitrin (B. W. & Co.). This precipitated a severe attack, so that I did not again repeat it.

CASE VIII. Patient, aet. 49.

Had passed the menopause at 47.

Complained of severe menorrhagia lasting 3 weeks. Pulse 80. Blood Pressure 140.

On P.V. examination, nothing abnormal was to be made out.

I curetted her under chloroform, and then gave her/

her 1 cc. pituitrin (B. W. & Co.) Scrapings were sent away for thorough examination. According to the report, there were no signs of a neoplasm.

She then received intramuscular injections of .5 cc. of pituitrin morning and night for two days, when bleeding entirely stopped. Patient then received 5 grain tablets of pituitrin morning and night together with calcium lactate gr V, and did not complain of any more haemorrhages. Some two years later she had a large ovarian cyst removed. She died two weeks later of broncho-pneumonia.

Before proceeding with some of my obstetrical cases I shall summarize my results and conclusions of these and other similar cases.

TABLE./

CASE.	BLOOD PRESSURE.			PULSE.		
	Before Injection.	After Injection.	Difference.	Before Injection.	After Injection.	Difference.
Shock.	100	120	20	100	66	34
Shock.	100	130	30	110	80	30
Shock.	100	120	20	116	80	36
Collapse.	85	120	35	116	76	40
Shock.	90	115	25	88	66	22
Collapse.	110	130	20	120	170	20
Shock.	95	120	25	92	84	8

The average increase of blood pressure was 25 and the average fall in pulse rate about 27.

These results, though few to judge from, convince me of the beneficial use of pituitrin in the treatment of shock.

Diuresis was noted to be increased in 4 cases out of the 7, i.e. in 57%. No doubt it may have been caused in Case IV by the brandy but very likely the pituitrin was largely the cause.

The vomiting in Case III was most likely due to the intoxication itself, although the pituitrin may also have aided by stimulating the stomach into contraction.

Eleven cases of constipation were treated on lines such as outlined in Case V and 10 experienced absolute relief.

It is possible, though not probable, that the entire effect was due to the liquid paraffin, and the massage which was recommended in each case, in conjunction with auto-suggestion, although out of 4 cases treated exactly the same, with a substitute of an injection of pure water and no tablets by the mouth, only one expressed himself as being relieved after 3 weeks.

My reason for attempting pituitrin in the case of/

of early Exophthalmic goitre was to see whether it was possible at this stage to negative the effect of thyroid hypersecretion by pituitrin. Though apparently beneficial in Case VI, the result is too inconclusive to give one an idea of the possibilities of pituitary extract in such cases. More experience would be needed for this.

Case VII presented a pale appearance, and her subnormal temperature and flabbiness made me try the effect of the pituitrin which failed. The case however seems interesting in view of the fact that Prof. Meakins had a case of Asthma in hospital, in whom the asthmatic attacks completely cleared up after receiving extract of thyroid gland. In this case it appears to be likely that the thyroid may have negatived the pituitary secretion, which was possibly the cause of the attacks.

I am strongly of opinion that the menorrhagia in Case VIII was due to hypopituitarism, not because the result of the scrapings proved negative to findings of malignancy and not entirely because she was relieved by the extract, but also because of the ovarian cyst. This might conceivably have caused an early change in the pituitary, which may have led to the symptoms mentioned.

OBSTETRICAL CASES.

CASE I. Patient, aet. 34. 1-para.

When I saw her she was bleeding profusely per vaginam. She was 9 months pregnant and had, about 9 hours before I saw her, had a severe motor accident.

On P.V. examination, the os was found to be the size of a threepenny piece. The membranes were ruptured by myself. This was followed by a markedly blood-stained flow of amniotic fluid. Two bougies were introduced, the membranes separated, as far up as possible, and the vagina tightly packed. Very slight pains followed, even after a tight abdominal binder was applied. Blood pressure was 135 and pulse 90. An hour later .5 cc. of pituitrin (B.W. & Co.) was given, followed in 10 minutes by another .5 cc. intramuscularly.

After 10 minutes Blood pressure rose to 145 and the pulse fell to 70.

Twenty-five minutes later severe pains came on and in two and a half hours a dead foetus was normally delivered. She made a rapid recovery.

CASE II. Patient, aet. 28. 2-para.

14 weeks pregnant. She was in a state of total collapse when I saw her, with severe uterine haemorrhage, which had lasted 10 hours, and a pulse of 120. The vagina was immediately tightly packed and one pint of warm saline given subcutaneously with mXXadrenalin. After 50 minutes the blood pressure rose from 110 to 130 mm. $\frac{1}{2}$ hour after the saline, 1 cc. of pituitrin having been given intramuscularly. The pulse fell to 100. Two hours later I arrived again, and was told that the patient had had some pains. She was not looking well, so I removed the plug to assure myself there was no more bleeding. Lying in the vagina, I found a piece of placental tissue. The os was sufficiently open to admit my index finger, with which I made sure that the uterus was empty, and contracting very well.

She made a rapid recovery after this.

CASE III. Patient, aet. 29. Nullipara.

She had a similar history to Case II, being 5 months pregnant. Her bleeding had lasted for 4 hours. Her pulse was 100 and her blood pressure 120. She was packed vaginally and put to bed. Twelve hours later, her pulse rose to 110 and her blood pressure fell to 110, the bleeding appearing/

appearing to be still continuing. I repacked the vagina and gave an injection of .5 cc. of pituitrin (P.D. & Co.) and of gr. $\frac{1}{8}$ of morphia.

In $1\frac{1}{2}$ hours time the entire placenta, and membranes came away, after which she made an uninterrupted recovery, her pulse having settled at 96 and the B.P. having risen to 130.

CASE IV. Patient, aet. 29. 6-para.

At the time when I saw her she had been in labour for over 48 hours, and had "felt no life for 24 hours". Palpation and P.V. examination revealed the true state of affairs. She had an impacted breach, though the os was fully dilated. She was in an exhausted state with a pulse of 108 and a blood pressure of 125. No foetal heart sound heard. I immediately gave her a hypodermic of gr. $\frac{1}{4}$ of morphia, and with the patient under chloroform brought down both legs of the child. One and a half hours later no uterine contractions made me give her .5 cc. of pituitrin (B.W. & Co.) and follow this up in 10 minutes with another $\frac{1}{2}$ cc. of the same. In 15 minutes a macerated foetus was born. The placenta was removed manually. Slight post partum haemorrhage was easily checked with a third intramuscular injection of .5 cc. pituitrin (B.W. & Co.). Except for a slight rise on the second day, of the temperature up to 100.6° F. she made a satisfactory recovery.

CASE V. Patient, aet. 38. 3-para. Attended on a farm by an old uncertified midwife.

Had post partum haemorrhage lasting $2\frac{1}{2}$ hours before I saw her. She was collapsed when I saw her, with a pulse of 118 and a blood pressure of 90. I immediately proceeded to pack the vagina tightly. She next received an intramuscular injection of 1 cc. of pituitrin (B.W. & Co.) and 1 pint of saline with 20 drops of adrenalin under the breasts. In 15 minutes the uterus hardened, the pulse fell to 86 and the blood pressure rose to 130. Some hours later the packing was removed and hot intra-uterine douches given. Three days later her temperature rose to 103° F. and remained high for some 5 days and then settled. She made a good recovery.

CASE VI. Patient, aet. 22. Nullipara. Attended by same midwife as in Case V. Had severe post partum haemorrhage last 6 hours.

When I saw her she appeared moribund, pulse 120 and scarcely perceptible. She immediately received a hypodermic injection of $\frac{1}{60}$ gr. of strychnine and of ether, with 1 cc. of pituitrin intramuscularly. Her pulse rate fell to 98. She was then tightly plugged vaginally, and received a pint and a half of saline/

saline subcutaneously. The foot of the bed was raised. Her blood pressure now was 90. I gave her another $\frac{1}{2}$ cc. of pituitrin (B.W. & Co.) and noted a marked rise of Blood pressure to 115.

She died however that night, i.e., about 8 hours after this.

CASE VII. Patient, aet. 36. 1-para.

Os fully dilated. Pains very weak.

Membranes intact. Blood pressure 135 mm. and pulse 98. I ruptured the membranes, and after waiting for about 40 minutes, as the pains were few and weak, I gave her an injection of .5 cc. pituitrin (B.W. & Co.) followed in 10 minutes by another .5 cc. Ten minutes later sharp pains came on, the blood pressure rising to 150, and in 20 minutes the child was born and ten minutes afterwards the third stage was over. Diuresis was a very marked feature.

CASE VIII. Patient, aet. 25. Primipara.

Labour very protracted. Patient exhausted. Os not fully dilated, but entire lower uterine segment well "taken up". She received 1 cc. pituitrin. Violent pains ensued: gr. $\frac{1}{6}$ of morphia relieved the pain to a very great extent, but did not interfere with the contractions.

In/

In 25 minutes the child was born, and 15 minutes later the placenta was expressed. Diuresis was not marked.

CASE IX. Patient, aet. 32. 6-para.

About 16 hours in labour, os size of sixpenny piece. Given .5 cc. infundin (B.W. & Co.). Blood pressure rose from 130 to 140, pulse remaining at 70 and contractions became stronger. Two hours later, the lower uterine segment being "taken up", i.e., when there existed no more a cervical canal she received another .5 cc. of infundin. In 15 minutes pains became severe and in half an hour, the child was born. The placenta followed in another half hour. A noted feature was the diuresis. She made an uneventful recovery.

CASE X. Patient, aet. 30. 2-para.

Had normally given birth to a full-time child. I saw her half an hour later. The placenta was not expelled, and I could not bring about expulsion by Credé's method, so I gave her 1.0 cc. pituitrin (B.W. & Co.). As this did not bring away the placenta, I decided to do so manually, but found the os greatly closed down over the afterbirth. After some 10 minutes I managed to remove the uterine contents under chloroform. She made an uneventful recovery.

CASE XI. After labour: The child much cyanosed, and in a state of animated suspension.

Resuscitation of many kinds being of no avail, in a few minutes, 1 cc. pituitrin was given into the abdominal wall. Artificial respiration was then resumed for about 5 minutes, with no result. A dose of 5 minims of Sheil's fluid was then injected into the abdominal wall. In a couple of minutes the child took a breath, followed by another, and in another minute it was crying lustily. It recovered completely.

SUMMARY AND CONCLUSIONS.

The effect of pituitary extract in these and other cases convince me, by the results obtained, that the drug has marked and definite therapeutic actions, by reason of which, it deserves to be placed amongst the ranks of the more valuable drugs.

Its properties are mainly:-

(a) It raises blood pressure. In a series of 92 cases the average rise was 30 mm. Hg.

(b) It slows the pulse rate. The average decrease in number, per minute, in 92 observations, was 17.

(c) It causes diuresis. This marked effect was noticed in 60 out of the 92 cases, i.e., in 55%, although the total amount of urine passed in 24 hours, was in 48 of these cases not increased.

(d) It causes an increase in the tone of the atonic intestinal tract.

(e) It dilates the pupils. In some 38 out of 92 cases, i.e., in 39% of cases this was clearly noticed.

(f) It causes increase, both in the length and strength/

strength of contractions of the gravid uterus of any stage, or at any rate, from the 14th week as noted in Case II. One feels justified in claiming that the pituitrin aided in the contraction of the uterus in this case, as sufficient time had elapsed between packing of the vagina and the injection of the pituitrin, to show that the mechanical means was not in itself sufficient to cause the uterus to expel its contents.

Its greatest effect upon the uterus however, is produced when labour has already commenced.

In view of these properties of pituitary extract, it may be advantageously used in the treatment of a variety of conditions.

One might classify the extent to which advantage may be taken of its Uses:-

(1) To cause increased contraction of the gravid uterus.

(11) To hasten labour.

(111) To overcome primary, and after appropriate treatment and attention, also secondary uterine inertia.

(IV) To stop uterine bleeding - accidental or post partum, when due to want of complete contraction of the uterus.

(V) To counteract and treat collapse in labour.

(VI)/

(VI) To cope with shock, due to any cause - in conjunction, when there has been severe loss of blood, with other treatment such as intravenous or subcutaneous saline injection or transfusion.

(VII) To assist intestinal peristalsis and increase the tone of the atonic intestine.

(VIII) To counteract the increased or irregular activity of the thyroid or ovaries in early stages in which they may cause menorrhagia.

In none of my cases did I experience:-

(a) Tetanic contraction of the uterus.

(b) Rigidity of the cervix.

(c) Raised temperature, which could be ascribed to the pituitrin.

(d) Foetal asphyxia when pituitrin alone was used. Occasionally, when combined with morphia, it produced various degrees of cyanosis in the child. When cyanosis and suspended breathing did occur, I did not find.-

(e) Stimulation of the foetal respiratory centre after injection of 1 cc. of pituitrin, as claimed by Prof. Kingston.

After failure to get response with pituitrin, a subsequent injection of Sheil's Fluid* was followed by/

* Sheil's Fluid:	Brandy	m.viii.
	Tinc. Belladon.	m.i.
	Liquor Strychnin.	m.i.

by an almost immediate reaction causing the child to breathe. Whether the pituitrin had "sensitized" the respiratory centre to respond readily to the fluid, I am not prepared to say.

CONTRAINDICATIONS TO ITS USE.

- (I) When the patient shows great reaction after receiving one dose.

In 3 cases out of 92, i.e., in about 2.8%, the patient had severe pains, headache, almost immediate vomiting followed in about 25 minutes by a rash which lasted about 12 hours.

- (II) In heart disease, especially mitral stenosis, where, in labour, it is essential to have an absolute minimum of strain to avert the disaster of heart failure.

- (III) When the blood pressure is already raised for some other reason, such as by kidney disease.

- (IV) In labour when there exists great disproportion between the foetal head and the maternal pelvis.

In cases however in which this disproportion is not very marked, it is wonderful, the amount of head-moulding and overriding of the perietals that occurs, and what a comparatively large proportion of such labours are successfully completed by pituitrin, aided by the forceps.

- (V)/

- (V) When, in labour, there exists an obstruction to the exit of the foetus, such as fibroid or ovarian tumours, anterior lip of the cervix, etc.
- (VI) When the foetus lies in certain malpositions, such as transversely, with the arm protruding through the vagina, and a much distended lower uterine segment, or in persistent mento-posterior cases.
- (VII) Early in the third stage of labour, when it may lead to great difficulties, especially if the placenta be adherent, or even merely retained as in my Case X.

SITE FOR INJECTION.

One has found equally good results when the drug is injected into the gluteal region or the upper arm, and not nearly so good when injected into the legs.

TIME TO GIVE PITUITRIN IN LABOUR.

It may be given any time after the entire cervical canal has been obliterated, irrespective of the size/

size of the os. The smaller the os, the smaller should be the dose of pituitary extract.

The thinner the lower uterine segment in unobstructed labours, the more marked is the action of pituitrin, in unobstructed labour.

If given (a) Early in the first stage, the pains are not materially increased, as noticed in 7 of my cases.

(b) Later in the first stage, contractions materially improve.

(c) End of first or early in second stage, labour proceeds very rapidly. This is the time when a dose of 1 cc. infundin shows itself of the greatest value.

(d) After the third stage, it causes satisfactory contraction of the uterus and controls haemorrhage.

METHODS IN WHICH USED.

As experienced by myself, pituitrin may be given.-

- A. Alone, in doses of 1.0 cc.
- B. Alone, in doses of .5 cc.
- C. In 1.0 cc. doses with morphia gr. $\frac{1}{6}$
- D. In .5 cc. doses, followed by .5 cc. pituitrin and morphia gr. $\frac{1}{6}$.
- E. With Scopolamine morphine narcosis.



A. One finds, as in Case VIII, that 1 cc. pituitrin undoubtedly increases the force of uterine contractions, but that it also greatly increases the severity of the pain.

Given before full dilatation of the os, its action is effective but not any more so than,

B. .5 cc. doses. When given early, the initial dose does not satisfactorily increase uterine contraction.

In a series of 20 cases however, second injections about 10 minutes later or even third injections, 20 minutes after the second of .5 cc. of pituitrin gave excellent response, with not nearly the amount of pain as in the A. cases.

C. and D. Morphia gr. $\frac{1}{6}$, given with the pituitrin does not seem to interfere with its action in any way. It greatly diminishes the suffering of the parturient woman, and is thus advantageously combined with pituitary extract. Single doses of 1 cc. infundin and gr. $\frac{1}{6}$ morphia are best given late in labour. The morphia should preferably precede the infundin by about 5 minutes. .5 cc. infundin may be given early, and followed by another .5 cc. with morphia gr. $\frac{1}{6}$ about 10-15 minutes later.

E./

E. Scopolamine-morphin administration to the patient does not hinder the action of pituitrin.

In these cases, it is best to give the pituitrin in 1 cc. doses, late, i.e., when the os is fully dilated, so as to ensure rapid delivery of the child which may already be suffering from the effects of the hyoscine or the morphia.

With the improvement in the use of pituitrin by the addition of the morphia, one might suggest that the former be never used, in the earlier stages at any rate, in larger doses than .5 cc. without its being combined with small doses of morphia, preceding it by about 5 minutes.

My experience with pituitary extract has been rather limited, and the results in many cases, if anything, rather inconclusive, leaving it rather difficult to interpret certain changes noted. I feel convinced nevertheless that it has the mentioned pharmacological actions which suffice to make it a valuable drug.

A great amount of knowledge of the pituitary is still lacking, and undoubtedly many of its properties and uses still undiscovered.

That the pituitary is closely associated with
the/

the rest of the endocrine organs is certain, but what the nature of this inter-relationship is, as also its more advantageous combination with other drugs, have still to be shewn.

This should however not bar its being used in labour at any rate, in preference to such drugs as ergot, over which it possesses the great advantage of at least diminished risk of tetanic contractions of the uterus.

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