THE ENDOCRINES IN THEORY AND PRACTICE

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EXTRACT OF THE POSTERIOR LOBE OF THE PITUITARY GLAND

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The posterior lobe of the pituitary gland contains at least two active principles of therapeutic value. These have been isolated as white powders free from protein. One of them acts upon the muscle of the uterus, and is therefore called oxytocin (quick-birth); the other constricts blood vessels, thereby raising the blood pressure, and has been named vasopressin. Oxytocin is 150 times and vasopressin eighty times as potent as the standard powder of posterior pituitary gland. Oxytocin has little or no action upon the blood vessels. Vasopressin has little or no action upon the uterus, but, in addition to constricting blood vessels, it modifies metabolism, controls the secretion of the kidneys, and can stimulate peristalsis of the alimentary tract. Certain extracts injected in large quantities into animals cause ulceration of the stomach.¹

As the separation of these two substances from the pituitary gland is complicated their price must be high; whenever, therefore, the effect of the second substance cannot do harm, an active extract of the gland may be used. The substances have been used therapeutically in the following conditions:

Oxytocin (Pitocin)	Vasopressin (Pitressin)
Insufficient contraction of the uterus	Transurethral resection of prostate gland Diabetes insipidus Xanthomatosis Hypoglycaemia Paralytic ileus Circulatory failure Haemoptysis Asthma

Its Use in Obstetrics

The main bulk of pituitary extract marketed is used by obstetricians to increase the strength of the contraction of the uterus and also to prevent or control post-partum haemorrhage. Thirty years ago Dale² demonstrated the action of pituitary extract upon the uterus, and a few years later Blair-Bell³ recorded his observations of its use in obstetric practice. The action of the extract is powerful, and if used incorrectly may lead to rupture of the uterus or asphyxia neonatorum. The main contraindications are: the first stage of labour, mechanical obstruction, complete inertia of the uterus, and a high retraction ring. If the patient has a high blood pressure, myocardial degeneration, an impaired renal function, or if the foetal heart sounds are feeble, it is wise to use pitocin rather than an extract which would contain vasopressin in addition.

Repeated small doses of pituitary extract have been employed to induce labour at full time; although several skilled observers have recorded high percentages of successes, disaster may follow its indiscriminate use, and all those who wish to avoid anxiety will reserve it for cases either in which the uterus is empty or in which

there is no doubt whatsoever that it can be emptied shortly after the injection of the extract.

Direct injection of pituitary extract into the uterus after the removal of the child by Caesarean section will control haemorrhage and cause firm contraction. It is alleged that uterine haemorrhage occurring at puberty or at the climacteric may be controlled by the injection of 5 units intramuscularly a few days before the anticipated date of menstruation; since there does not appear to be any physiological explanation of this action its success must not be expected invariably.

Its Use as a Haemostatic

Pituitary extract has been employed to produce temporarily a small bloodless region, and recently has been reported⁴ as helpful in the removal of the prostate gland piecemeal through the urethra, especially when the lobes of the prostate are large. Its use, however, increases the length of the operation, because the cystoscope must not be removed until the pituitary extract has ceased to act and the surgeon is satisfied that haemorrhage will not occur.

Diabetes Insipidus

The polyuria of diabetes insipidus, in the great majority of cases, can be controlled by injections of pituitary extract or pitressin.

(All the evidence at present suggests that vasopressin is only one substance with multiple actions; but it is only a few years ago that the extract of the posterior lobe of the pituitary gland was considered to contain only a single active principle.)

Administration by the mouth of immense doses of dried pituitary gland or extract, even when protected from the action of gastric juices by suitable coating, proves useless in the treatment of diabetes insipidus. Subcutaneous injection is perhaps the most efficacious method. Continuous injection of a solution of pitressin proved that only small quantities are required in the circulation; therefore the greater the number of injections in the twenty-four hours the less the total quantity necessary to control diuresis. On the other hand, the larger the dose the longer its action, but the size of the single dose has to be kept below that which will lead to discomfort. The optimum dose is the largest which will not make the patient "turn green," feel faint, or suffer intestinal pain which is followed by an action of the bowels. The injections should be timed to ensure an uninterrupted night's rest. Quite frequently diuresis in untreated diabetes insipidus is less during the night than during the day, and may be diminished still further by a soporific. This latter fact was for a time considered to be evidence in favour of diabetes insipidus being due to polydipsia with resultant polyuria, but since obstruction of the ureters in animals deprived of the posterior lobes of their pituitary glands abolishes thirst, the explanation of the action of soporifics must be along different lines.

Although extracts of pituitary gland are standardized, there nevertheless seems to be some variation in their anti-diuretic properties. It is wise, therefore, for accurate comparative observations to be made upon the urinary output when the same quantities of different makes of pituitary extracts are injected.

Frequent injections may be avoided by adopting Strauch's method of repository injections. Strauch⁵ injected eight times the usual dose of pituitary extract of fifteen times the usual strength. The formula he used consisted of 19 c.cm. of the extract emulsified with 2.5 c.cm. of olive oil, 0.2 gram of metacholestearin, and 0.3 gram of myricin. A single injection controlled thirst and diuresis from three to six days.

Fortunately the active principle, vasopressin, is absorbed through the nasal mucous membrane. This permits a variety of methods of administration—a nasal spray; a pledget of lint soaked in pituitary extract placed in contact with the turbinates; the use of a snuff consisting mainly of finely powdered pituitary gland which has been dried in acetone. The most popular method at present is the snuff, which, when taken every four hours, controls diuresis quite satisfactorily. Occasionally, however, this snuff causes asthma, probably due to the protein it contains. This complication can be met by using a snuff consisting of vasopressin 1 per cent. and lactose 99 per cent.

An extract of the pars intermedia containing a substance which acts neither upon the muscle of the uterus nor upon the blood vessels, but possesses a powerful action upon melanophore cells, has been alleged to control diuresis⁶ in diabetes insipidus when injected in doses of 1,000 phoxinus units. This substance, which has been called "intermedin," has failed even in larger doses in several cases.⁷ It has been suggested that when it controls diuresis it is due to a contamination with vasopressin.

Xanthomatosis

Vasopressin diminishes the cholesterol content of the blood following a meal rich in fat, and a deficiency of it is associated with hypercholesterolaemia, which, in turn, may lead to a deposit of cholesterol not only in the bones but also in the posterior lobe of the pituitary gland, thus establishing a vicious circle. It follows, therefore, that those cases of diabetes insipidus with hypercholesterolaemia not only should be given as much vasopressin as they can stand, but also should be placed upon a diet poor in fat and rich in carbohydrate, and perhaps be given some insulin. In addition, x-ray therapy should be applied to the sella turcica, since the rays are found to disperse deposits of cholesterol in bones.

Hypoglycaemia

On theoretical grounds pituitary extract is preferable to adrenaline in the treatment of hypoglycaemia, because adrenaline has been poured out into the blood automatically upon the sugar content falling; its action is to liberate sugar from the glycogen in the liver, whereas vasopressin has a distinctly antagonistic or neutralizing effect upon insulin. Ten units is the usual dose of pitressin administered in hypoglycaemic coma.

Paralytic Ileus

It has been mentioned above that, following the injection of pituitary extract or vasopressin in the treatment of diabetes mellitus, an action of the bowels is an annoying accessory effect. In certain conditions this property of pituitary extract may prove of great value. Vasopressin in small doses—3 to 5 units—tends to maintain the tone of the bowels, thus preventing an accumulation of gas. Larger doses cause active peristalsis and may give rise to pain; it is therefore wiser to give repeated small doses at intervals of four hours. It is scarcely necessary to add that on no account may pituitary extract be administered if there is the faintest suspicion of mechanical obstruction.

Circulatory Failure

Since pituitary extract acts directly upon the plain muscle of the blood vessels it may prove of great value in combating collapse provided the heart muscle is normal. It has been used in shock and also in cases of severe pneumonia, in which blood pressure has been low.

Haemoptysis

Vasopressin has been prescribed in haemoptysis,⁸ because it not only increases the coagulability of the blood,⁹ provided no great volume of blood has been lost, but also is alleged to reduce the pressure of the blood in the pulmonary circulation. This latter action has not been proved in man. In some animals it reduces the flow of blood through the coronary arteries, and thus diminishes the strength of the heart beat, and since it does not constrict the pulmonary vessels the blood pressure falls.¹⁰ In the cat, however, the effect is the reverse; it increases the flow of blood through the coronary vessels and the pulmonary blood pressure rises.

If vasopressin is proved to reduce the blood pressure in the pulmonary circulation in man it should be preferable to aconite, which has a similar effect. Aconite, however, in addition causes a fall of blood pressure in the systemic circulation, and thus makes the patient feel faint.

Asthma

Pituitary extract was introduced as a treatment for asthma because it was supposed to relax smooth¹¹ muscle fibres. This is at least doubtful. The view taken at present is that pituitary extract increases and prolongs the action of adrenaline, and since there is no physiological action to account for this it is alleged to sensitize the tissues to the action of adrenaline.

Until some satisfactory explanation for its alleged beneficial action in haemoptysis and asthma is forthcoming pituitary extract should be employed only when very careful observations can be made, and these should be recorded with the object of establishing or exploding its claim to utility in these conditions.

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A. Mouchet (*Presse Méd.*, September 16th, 1936, p. 1449), who records an illustrative case, states that in forty-five cases of operation for typhoid peritonitis which have been published since 1924 the recovery rate was 51 per cent. This figure is lower than that recorded in 1933 by Soupault, who had a recovery rate of 77 per cent. Mouchet, however, has excluded cases of peritonitis without perforation and localized peritonitis, which is sufficient to account for the difference in the results. The recovery rate in Mouchet's series is higher than that of 38 per cent. recorded by Gueullette in 1924, of 30 per cent. by Lenormant in 1931, and of 17 per cent. by Jaki in 1925. Mouchet's case is that of a girl aged 18, in whom laparotomy was performed on November 18th under ether anaesthesia by a subumbilical incision, in the second week of typhoid fever. Perforation was found in the ileum, 25 cm. from the caecum, and an enterostomy performed by Witzel's method. On February 4th the enterostomy wound was closed and complete recovery took place.