THE ACTION OF PITUITARY EXTRACTS.

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by

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THE ACTION OF PITUITARY EXTRACTS.

I. INTRODUCTION.

From earliest times the organs and tissues of animals have been employed as medicines in the treatment of disease and with little more than superstition to support their claims to merit. Recent years have seen a revival of interest in organo-therapy. Experimental investigation has shown that certain animal substances possess properties of great therapeutic value as is notably the case with the thyroid gland in the treatment of myxoedema and cretinism.

To Brown-Sequard much of the credit for the important results of recent work in this subject is due. He contended that all the glands give, by internal secretion to the blood, principles essential to the general good health of the body. That the thyroid gland secretions are necessary to life is well known, for, if all thyroidal tissue be removed, death invariably ensues. This is due to arrest of secretion, but excess of secretion is also detrimental to good health. It is more than probable that these glands so work in groups that their secretions in health balance each other and function as toxins and antitoxins. If one gland or group of glands 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.

Experimental investigation in the case of the thyroid and suprarenal glands has contributed such valuable results to therapeutics that physiologists have directed their attention to the study of the pituitary body and although nothing definite as to its functions is as yet known, the clearly important results of recent research hold out the promise that in the extracts of this organ we shall eventually have a therapeutic agent in no wise inferior to these other glandular substances.

That the pituitary body produces internal secretions necessary to life and good health is certain for removal is followed by a train of definite 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 Schiff\(^1\) found 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 effects of the administration of the extract manifest themselves in a marked rise of
blood pressure and slowing of the pulse directly due to increased cardiac contraction and arterial constric-
tion. Schafer and Oliver\textsuperscript{2} first pointed this out and they also discovered that the effect remained after the central nervous system had been destroyed proving that the action is directly on the muscles and without relation to their innervation.

Howell\textsuperscript{3} showed that an extract made from the anterior lobe did not produce this result but that the extract of the posterior or infundibular lobe alone possessed this property. Later, Schafer and Vincent\textsuperscript{4} confirmed this observation.

Dale\textsuperscript{5} found that the infundibular extract caused uterine contractions. Bell and Hick\textsuperscript{6} confirmed this and also discovered when experimenting on pithed rabbits that violent peristaltic movements were set up in the intestines.

Schafer and Magnus\textsuperscript{7} and, later, Schafer and Herring\textsuperscript{8} observed that the extract caused marked diuresis by reason of a selective action on the vessels of the kidneys.

Although we are practically ignorant of the functions of the pituitary gland it is evident that its secretions are of the greatest physiological importance and that they contain an active principle or principles possessing properties which warrant the belief that a remedial agent in no way inferior to other animal ex-
tracts has been placed in our hands.

As the extract raises the blood pressure and keeps it raised for several hours it should be indicated in conditions of lowered blood pressure such as shock, post operative and otherwise, and in certain cases of cardiac debility and disease.

Its action on the intestinal muscle would suggest that in paresis and atony of the intestines it might be of great service.

Uterine haemorrhages and diseases such as endometritis suggest a field for its use.

In exophthalmic goitre there is hypersecretion of the thyroid and probably excessive formation of a toxin. Good results have been obtained in this disease from the administration of pituitary extract. It may be that the pituitary is the balancing gland to the thyroid and that in administering the extract we are supplying the antitoxin to the excess of toxin produced in that disease.

The difficulty of interpreting the results of administration of pituitary extract is great. Experiments have proved it to be a highly active substance but its therapeutic value can only be learnt from extended clinical trials.

In my thesis I propose to give a résumé of our present knowledge of the subject and the results of my own personal experience.
II. HISTORICAL.

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, of comparatively recent date, 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. It was even seriously suggested that the main object of its existence was to act as a pad for the protection of the trachea, or, to improve the contour of the neck.

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 Suprarenal Glands. His theory is the most plausible and likely of any advanced and is probably correct, but years elapsed before it received general recognition. Meanwhile, although Addison had really interpreted 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. Although organotherapy has been practised from the earliest times it has now been confirmed on a scientific basis as the outcome of modern research. According to the doctrine of internal secretion, the ductless and other glands secrete specific substances which pass into the circulation and influence all the cells of the organism in their own peculiar way. If through disturbance of a gland there is increase or diminution of its secretion a disturbance in other tissues is produced, showing that the various glands and tissues of the body are inter-dependent. Within the last few years much research has been expended on the long-neglected ductless glands and the results have been surprising indeed. Incomplete and scanty though our knowledge at present is, we have already learned that they occupy a most important place in the regulation of the health of the body, and different observers have proved by the removal of the thyroid and suprarenal glands, that these structures are necessary to life.

When one considers the naked eye and microscopic appearances of these structures, it seems incredible that bodies of such complex organisation and evident cellular activity, should have been so summarily dismissed as unworthy of serious attention.

Modern organotherapy 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 preparations from the corresponding organs of healthy animals to supplement the deficiency. The condition known as cachexia strumipriva, which is brought about by removal of all thyroidal tissue is an artificially induced myxoedema, and the symptoms in both are exactly 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, results in the changes of mind and body characteristic of myxoedema. The acquisition of this knowledge was the first great triumph of the physiologists in their research on the functions of the ductless glands.

In 1894 Oliver and Schäfer published the brilliant results of their work on the Suprarenal Glands, showing that the extract made from these organs possessed properties quite as wonderful as those of thyroid extract. Some observers have noted beneficial results in the treatment of Addison's Disease from the administration of suprarenal extract, but, apart from this, the active principle of the secretion of the gland has been discovered and found to be a substance possessing remarkable properties. Its action 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. Contraction 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 suprarenal glands, life is impossible. Several observers, including Paulesco have recently demonstrated that in this respect the pituitary gland is of equal importance. In 1895, Oliver and Schafer 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 the thyroid and suprarenal glands. These effects manifest themselves in a pronounced rise of blood pressure, in profuse diuresis, in slowing and strengthening of the heart and in marked tonic contractions of the uterus.

Although the chemical nature of the active substance of the suprarenal secretion has been accurately ascertained, the attempts to isolate the active principle of the pituitary secretion have so far given no satisfactory results, but, as in the action of the two extracts there are several points of similarity, it has been suggested that the active principle is the same in both cases. Both raise the blood pressure through constriction of the blood vessels, both cause contraction of the uterus, and in both cases the organ
concerned is formed of two parts, histologically and embryologically distinct. In both, the part histologically glandular in appearance yields an inactive extract, whereas the other, developed in each case in connection with the nervous system, yields substances which have marked effects upon the cardio-vascular system. The similarity is, however, only superficial. With regard to the pressor action, the suprarenal extract produces its effect through the sympathetic nervous system but 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. It is to be noted in this connection that, whereas suprarenal extract increases the rate of the pulse, pituitary extract decreases its rapidity, and, its action is much more prolonged, in striking contrast to the fleeting effect of suprarenal extract. The latter 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 contractions in all species and in all conditions of functional activity. Howell noted that during the period of action a second injection of pituitary substance does not increase its effects. Immunity of this kind is not produced by suprarenal extract. But, the first dose
of pituitary substance confers no immunity against suprarenal extract which, given after the pituitary effect has almost, or quite, passed off increases arterial pressure to no less an extent and seemingly for a longer period than it does in the absence of a pituitary injection as was shown by Mummery and Syme. The most striking difference, however, is in relation to their effects on the kidney; for while suprarenal extract produces constriction of the renal vessels and diminution of secretion, pituitary extract causes dilation of the vessels of the kidney and increased secretion. There is thus every reason for concluding that the pituitary active principle is quite different from that of the suprarenal and although it has not yet been isolated it is evident that given, as it only can be at present, in the form of an extract of the gland, it must have many important therapeutic applications.

Bate says the infundibular secretion is undoubtedly antidotal to excessive thyroidal action and in this connection it is to be noted that cases of exophthalmic goitre have benefitted by its administration. For the shock following the administration of anaesthetics it has been proved to be a most valuable agent. In uterine haemorrhages it is reported as being highly efficient and in cardio-vascular diseases with low blood pressure the results have been most satisfactory. In the treatment of hay fever and asthma it is a most
successful remedy, the results being much more enduring than those obtained from the use of suprarenal extract. Its therapeutic value 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 nowise inferior to the better known glandular extracts.
III. ANATOMY AND HISTOLOGY OF THE PITUITARY BODY.

Projecting downwards from the outer aspect of the floor of the third ventricle of the brain, and behind the optic chiasma is the stalk-like process called the infundibulum which expands at its apex into the posterior of the two lobes of the pituitary gland. This rests in the depression of the sphenoid bone called the sella turcica, and is closely invested by the dura mater.

The pituitary body is an egg-shaped structure, greyish red in appearance, and weighing, in health, on the average, 0.6 gram. It 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 (Rathke's Pouch) of the ectoderm of the buccal cavity, losing, at a later stage, all connection with the mouth. 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.

Between the anterior and posterior lobes is the intraglandular cleft containing a yellowish fluid which
is probably secreted from the cells adjoining the cleft.

The posterior lobe consists of two parts, the pars intermedia and the pars nervosa.

The pars intermedia bounds the intraglandular cleft posteriorly, and consists of an epithelial layer a few cells deep. It is derived from the epithelium of the invagination which has formed the anterior lobe.

The pars nervosa is developed as a prolongation of that part of the embryonic brain which becomes the third ventricle. In some animals it is hollow throughout life, in others the infundibulum alone remains hollow, while in most, including man, the extension of the cavity becomes obliterated, and we have the stalk shaped infundibulum, with merely traces of a cavity, expanding into the solid posterior lobe.

In structure, the pars nervosa consists of a groundwork of ependyma and neuroglia cells and fibres containing islets of epithelial cells which are similar to the cells of the pars intermedia, many of which contain globules of colloid-like material. Near these islets of cells are globular masses of this colloid matter in tubules and vesicles extending from the pars intermedia to the infundibulum. This substance probably represents the secretion of this lobe, and is elaborated as a result of glandular activity. It passes into the capillaries and probably into the third ventricle. It is insoluble in water, alcohol, and ether, and does not yield gelatin on boiling.
The cells of the anterior lobe are of different kinds. Some of them stain badly, chromophobe cells, and others are chromophile, either eosinophile or basophile. The existence of fatty granules in the cells has been shown. It is possible that the chromophobe cells are in an exhausted or resting state, and various stages of activity are recognised as indicated by the presence of eosinophile and basophile cells.

**PHYSIOLOGY OF THE PITUITARY BODY.**

The pituitary body is essential to life. It has been removed by Paulesco, Cushing and others, and in all instances the result has been great depression, apathy, muscular weakness and tremors, dyspnoea, and progressive emaciation leading to fatal cachexia.

Two opposite sets of symptoms follow from diminished and excessive pituitary activity respectively. If insufficiency is produced by the administration of a cytotoxic serum for that structure, emaciation, muscular wasting and disappearance of the panniculus adiposus, great muscular weakness, a plantigrade method of progression, and some modifications of the skeleton are brought about. Similar symptoms result if the whole or part of the anterior lobe be removed, all the appearances being those of genital infantilism, a condition almost always associated with destructive pituitary disease.
Excessive pituitary activity is accompanied by high arterial tension, polyuria, glycosuria, disturbances of nutrition, emaciation, in some cases obesity, in other cases hypertrophic processes leading to gigantism or acromegaly, certain psychical phenomena, somnolence, genital and frequently thyroid insufficiency. That the disease of acromegaly is closely associated with changes in the pituitary body producing hypersecretion is now regarded as absolutely certain. Another opinion that has received general acceptance is that gigantism and acromegaly are one and the same disease, only differing in respect of the age at which each begins. Gibson, in an address to the Norwich Med-Chir. Soc., stated that the one constant factor in acromegaly is hypertrophy of the pituitary body, and he referred to Cunningham's view, that when the pathological condition begins early in life, before the union of the shafts of long bones and their epiphyses has taken place, gigantism is the result, whereas, when the pituitary change does not take place till adult life, acromegaly results.

It is to be concluded that the pituitary body supplies a secretion to the blood necessary to life and health. Histological observations would indicate that the anterior lobe is the active portion of the gland, and that the posterior is merely a vestigial structure, but physiological experiments indicate the
opposite. Howell showed that the substance, causing the marked effects on the cardio-vascular system, is yielded only by the posterior lobe, the anterior or glandular lobe being in this direction inert. Schiff's experiments by the administration of pituitary extracts showed that an intensive increase of the entire secretion of phosphoric acid takes place with only slight increase of nitrogen, which would indicate an influence upon the metabolism of bone. When we consider the modifications of the skeleton in disease of the anterior lobe as exemplified in gigantism and acromegaly, it is probable that the secretion from this part of the pituitary body exerts an influence on the growth and nutrition of bones, whereas the posterior lobe provides a secretion which has marked effects on the heart and blood vessels.

It has been suggested that the pituitary gland can vicariously take the place of the thyroid. After thyroidectomy, and in myxoedema, the pituitary gland becomes enlarged, and by some it is believed that this indicates a complementary function on its part. This theory seems, however, to be negatived by the physiological effects of the administration of their respective extracts. Thyroid produces no obvious result on the contractions of the heart, whereas pituitary greatly increases their force. With thyroid there is a fall of blood pressure, but with pituitary, on the
other hand, there is a great rise. It has been suggested that the enlargement is more probably caused by toxic reaction and disturbance of interglandular equilibrium.

One of the most prominent theories of the pituitary function is that its secretion is antitoxic. It was at first believed that acromegaly was due to more or less complete suppression of the internal secretion of the pituitary body. But, as in exophthalmic goitre we have excessive thyroid secretion, so in acromegaly, it is now believed that we have hypersecretion of the pituitary. In the introduction to this thesis I stated it was probable in health the ductless glands so work in groups that their secretions balance each other and function as toxins and antitoxins, and that when one gland or group of glands fails to respond, there is excessive formation of a toxin whose natural antidote is deficient, and the symptoms, in part at least, are the effects of this toxin. There is strong ground for believing that the thyroid and pituitary glands are in their functions very intimately associated in some directions. In this relation it is to be noted that in exophthalmic goitre, where we have excessive secretion of the thyroid, administration of thyroid extract does not effect improvement but the opposite, whereas, with pituitary extract, Renon and Parisot have obtained considerable improvement. After
three weeks treatment, Renon brought about reduction of the goitre, of tachycardia, exophthalmic tremor, and perspiration, with marked improvement of the general health. Likewise, in acromegaly, the symptoms of which greatly resemble those which have been described as indicating excessive action of the pituitary, Kerry and others obtained marked improvement by thyroid treatment, while the administration of pituitary as shown by Marinesco has had no notable effect on the symptoms supposed to depend on failure of the metabolic functions of the secretion. It would seem likely, therefore, that in addition to their other functions, the pituitary and thyroid are balancing glands, and that, when in disease of the one, benefit is derived from administration of an extract of the other, it is because we are supplying the natural antitoxin to the excess of toxin produced by the opposing gland.

It is probable that several active principles are produced by the different parts of the pituitary body, and that these, circulating in the blood along with "hormones" from other organs, bring about a correlation of the functions of the organs concerned, and by their balanced and mutually re-acting stimulus maintain the general health of the body. The physiology of the pituitary gland is very imperfectly understood, but we know that its existence is necessary to life, and that it supplies an internal secretion to the blood. This
secretion tends to increase the contractions of the heart and blood vessels, and perhaps exerts an influence on the nutrition of some of the tissues, particularly bone. It is also very probable that it possesses an antitoxic action.

**PATHOLOGY OF THE PITUITARY GLAND.**

Pathologically increased activity of the pituitary body expresses itself chiefly as a process of overgrowth leading to gigantism when beginning early in life, and to acromegaly when originating in adult life. Diminished activity, on the other hand, when beginning in youth is characterised by the signs of genital infantilism, and when in adult life, by a tendency towards the loss of the characteristics of adolescence.

Simple hypertrophy may, in some cases, be the cause of hyperpituitarism, and simple atrophy in others, the cause of hypopituitarism, but a tumour affecting the gland is the lesion to which one or other of these conditions is most naturally attributed. The most common alteration is a combination of a cystic, fibroid, or colloid, degeneration with a hyperplasia of the functionating cells, giving rise to adenoma or the so-called struma of the pituitary body. As might be expected, the symptoms caused by such a condition are those of hyperpituitarism. Sarcomata are also of frequent occurrence, but it has been shown that these
are often derived from the epithelium of the gland, and are probably malignant degenerations of the hyperplastic tissue of adenoma. It is to be noted that the anterior lobe is especially involved by new growths.

Cases of undoubted carcinomata and sarcomata have been observed, and gummata, tubercles, and lipomata have been described. These lesions are sometimes accompanied by symptoms of hypopituitarism and sometimes by symptoms of hyperpituitarism. In the former case it may be inferred that the functional cells are destroyed and replaced by some other tissue, while when the latter phenomena result, a hyperplasia of the functioning cells may be assumed to be present.

A case reported by Hochenegg is of much importance in throwing light on the relationship of a pathological condition of the gland and hypersecretion. A tumour, pathologically diagnosed as adenoma of the pituitary was removed from a female patient. Relief of the symptoms due to mechanical pressure was obtained, but, much more remarkable, all the acromegalic symptoms had practically disappeared a month after the operation.
IV. CHEMICAL COMPOSITION OF THE PITUITARY GLAND AND PITUITARY EXTRACTS.

It is to the posterior lobe of the Pituitary Gland that recent research has been directed and it is with extracts of this lobe that the most striking results have been obtained. Schafer and Oliver discovered that extracts of the whole gland produced, when injected intravenously, a great rise of blood pressure. Howell showed, later, that the substance causing this rise was yielded only by the posterior or infundibular lobe, the anterior in this respect being inert.

It has been already described that 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 the active principle and that the nervous elements are in no wise connected with its production for Osborne and Vincent have shown that extracts made from ordinary nervous tissue, whether of grey or white matter, mixed or each separately, have no pressor or blood pressure raising action.

The chemist has as yet been unsuccessful in discovering the chemical constitution of the active principle. Allers endeavoured to prove that it is of the same composition as that of suprarenal extract. He found that on heating pituitary extract with caustic...
soda he observed the smell of phosphoretted hydrogen and supposed that a substance was present which resembled the active principle of suprarenal extract, but he was unable to obtain the known reactions of adrenalin. Sufficient proof of their being two different substances has already been given in Section II of Thesis.

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 precipitated from this solution by trichloracetic acid and gives the biuret, xanthoproteic and Millon's reactions. It is not precipitated by saturation with a neutral salt. 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 recent discovery establishing the possession of a similar type of activity by the pressor bases of the extracts of the suprarenal glands, ergot and putrid meat is of great importance for it is probable that when the active principle of the infundibular extract is synthesized it will be found to bear a close relationship to these in its structural formula.

Dixon and Taylor prepared extracts from placentae 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 Dixon and Taylor believed that the active principle grew simultaneously with the placenta and was the natural stimulus for the production of labour. But, in 1906, Abellous proved that similar symptoms were produced when extracts made from putrid meat were injected into the blood stream. In 1909, Barger and Walpole identified the pressor bases in the extract of putrid meat and found them to be the following organic amines, phenylethylamine, para-hydroxyphenylethylamine and isomylamine. Rosenheim 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 recently by Barger and Dale that para-hydroxyphenylethylamine which is one of the pressor bases of putrid meat extract is also the chief active principle of aqueous extract of ergot. It is very nearly related in chemical structure to the supra-
renal active principle and on administration produces very similar results but its effects are slower and more persistent. 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 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. In all likelihood the chemist will in the near future be able to synthesise the active principle of the infundibular lobe of the pituitary body and it will probably be found to be an organic amine closely related to those which have been described.

The chemical formula of the active principle of the suprarenal gland is: \((\text{OH})_2\text{C}_6\text{H}_3\text{.CH(OH)CH}_2\text{.NHCH}_3\).

The chemical formula of para-hydroxyphenylethylamine is: \(\text{OH.C}_6\text{H}_4\text{.CH}_2\text{CH}_2\text{NH}_2\).
V. THE PHARMACOLOGY OF THE PITUITARY GLAND

AND PITUITARY EXTRACTS.

It has been already stated that the two lobes of the Pituitary Body are not of the same physiological value. It is with the posterior or infundibular lobe that most investigators have concerned themselves, but the statement that the anterior lobe is of no functional importance is rather difficult of acceptance. Falta \(^{29}\) 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 good evidence for associating disease of the anterior lobe with acromegaly and gigantism, and Schiff \(^{30}\) 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 the posterior or infundibular lobe that the most striking results have been obtained and it has already been mentioned that 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 contraction of the uterus. The active substance has not yet been isolated and at present we have to rely on the anatomical structure to provide us with it. The methods of administration which produce the general phenomena in characteristic rapid manner are intravenous and intramuscular injection. It may be given by the mouth and rectum and hypodermically but the active principle diffuses through animal membranes very slowly and is destroyed by pancreatic digestion. It is slowly absorbed from the stomach.

**ACTION ON THE HEART AND BLOOD VESSELS.**

In 1895 Schäfer and Oliver working with an extract of the whole gland produced a rise in blood pressure by intravenous injection. Howell showed that the anterior lobe had nothing to do with the result but that it was only an extract made from the infundibular portion of the gland which possessed the property of bringing about this increase of pressure. This observation was subsequently confirmed by Schäfer and Magnus.

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 has been given 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 pituitary extract, five minutes after, fif-
teen minutes after, half an hour after, and then hourly for four hours.


of Duncan Flockhart's

<table>
<thead>
<tr>
<th>Extract</th>
<th>84</th>
<th>125mm</th>
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<tbody>
<tr>
<td>5 mins. after injection.</td>
<td>80</td>
<td>130mm</td>
</tr>
<tr>
<td>15 mins. after injection.</td>
<td>80</td>
<td>135mm</td>
</tr>
<tr>
<td>30 mins. after injection.</td>
<td>80</td>
<td>130mm</td>
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<tr>
<td>I. 1 hour after injection.</td>
<td>74</td>
<td>130mm</td>
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<tr>
<td>2 hours after injection.</td>
<td>72</td>
<td>120mm</td>
</tr>
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<td>3 hours after injection.</td>
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<td>120mm</td>
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<td>4 hours after injection.</td>
<td>60</td>
<td>120mm</td>
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</tbody>
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Before injection of 1 c.c.

of Pituitrin (Park, Davis & Co). 78 110mm |

II. 5 mins. after injection. 74 115mm |

| 15 mins. after injection. | 72 | 125mm |
| 30 minutes after injection. | 70 | 120mm |
| 1 hour after injection. | 66 | 115mm |
| 2 hours after injection. | 66 | 115mm |
| 3 hours after injection. | 66 | 100mm |
| 4 hours after injection. | 68 | 100mm |

III. Before injecting 1 c.c. of

Burroughs Welcome & Co's

<table>
<thead>
<tr>
<th>Extract</th>
<th>120</th>
<th>130mm</th>
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<tbody>
<tr>
<td>5 mins. after injection.</td>
<td>106</td>
<td>140mm</td>
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<tr>
<td>15 mins. after injection.</td>
<td>106</td>
<td>150mm</td>
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</tbody>
</table>
Pulse. Blood Pressure.

30 minutes after injection.---102------140mm.
2 hours after injection--------106------156mm.
3 hours after injection--------106------150mm.
4 hours after injection--------100------130mm.

IV. Before injecting 1 c.c.

Pituitrin------------------------88------130m.m.
5 mins. after injection---------88------140mm.
15 mins. after injection--------78------150mm.
30 mins. after injection--------72------140mm.
2 hours after injection--------70------135mm.
3 hours after injection--------72------130mm.
4 hours after injection--------68------130mm.

V. Before injecting 1 c.c.

Duncan Flockhart & Co's

Extract.------------------------100------135mm.
5 mins. after injection--------106------150mm.
15 mins. after injection--------102------160mm.
30 mins. after injection--------98------155mm.
2 hours after injection--------92------145mm.
3 hours after injection--------88------135mm.
4 hours after injection--------88------130mm.

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. Frequently I have found the pulse remain below its normal rate for considerably more than twelve hours. This may proba-
bly be accounted for by the existence of a depressor as well as a pressor substance in the extract and that it is much more prolonged in its action than is the latter.

Oliver and Schäfer demonstrated that the increase in blood pressure is due to a constriction of the blood vessels and augmentation of the cardiac contractions and that these conditions persist after destruction of the central nervous system. Howell's experiments agreed in their results with Schäfer and Oliver's observations. He found that injection of an extract of the infundibular lobe caused a slowing of the heart and marked rise in blood pressure with the vagi intact, and with the vagi divided or after an injection of atropine less pronounced slowing of the heart but still the rise in blood pressure.

Cyon and Liven also found that the action of pituitary extract was manifested in a great increase in the strength of the heart's beats, a decrease of their frequency and in an increase of the blood pressure. Cyon showed that the section of the vagi, either before or after injection had little influence on the results obtained and that atropine did not inhibit the retardation produced by the pituitary extract except in very large quantities.

It is to be concluded from the results of the investigations of these observers that pituitary extract
causes a rise of blood pressure due to arterial constric-
tion which takes place independently of innervation by
the sympathetic system inasmuch as the effect is pro-
duced after destruction of the central nervous system.
If there were any relation between the two we would
expect increased frequency and force of the heart beat
corresponding to the effect of the cardio-accelerator
nerves but this is not the case, the beat of the heart
usually becoming slower even after section of the vagus.

It is known that the arterioles of the lungs which
receive no constrictor fibres from the sympathetic
system do not respond to the injection of suprarenal
extract like the rest of the arterial system but that
on the contrary they become engorged on account of the
diminution of the capacity in the other vessels; with
pituitary extract on the other hand the pulmonary art-
erioles are affected in common with those of the system
generally.

On treating sections of the main branches of the
pulmonary artery as isolated organs, Meyer\textsuperscript{35} and Langen-
dorf\textsuperscript{24} obtained definite constrictor results with supra-
renal extracts but Dale\textsuperscript{35} concluded that the sympathetic
nerves send motor fibres to the muscular walls of the
pulmonary artery and its main branches, and pointed out
that Brodie and Dixon showed that the muscular coats
of the pulmonary arterioles are not under the control
of the sympathetic nerves, but that the innervation stops short of them. Dixon and Dale in their experiments with the object of determining the effect of pituitary extract on the peripheral pulmonary arterioles perfused the lungs with Ringer's Solution. After observing that the active principle of suprarenal extract or para-hydroxyphenylethylamine caused only a slight acceleration of the rate of perfusion, loc. of pituitary extract was introduced to the solution. The result was a decided retardation of the outflow, or in other words, vaso-constriction was produced in vessels which are independent of sympathetic innervation, and in which the suprarenal extract failed to produce it.

There is not as yet complete agreement as to the innervation of the coronary arteries. Mass believes that they receive vaso-constrictor fibres from the vagus, and others have supported him in his contention. Schäfer on the other hand could find no evidence of vaso-motor nerves to these arteries and observed no constriction of them under the influence of suprarenal extract. Elliot and others have confirmed this observation. 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
The nature of the action of pituitary extract on the heart according to Golla appears to be a prolonging of systole rather than of diastole. Cleghorn showed that in an isolated heart, immediately after injection, systole becomes slightly slower and more vigorous, and later, weaker than before the injection. The action on the heart beat cannot be compared to the effect of accelerator nerves or of suprarenal extract, but is probably due to direct action on the sarcoplasm and to the altered rate of coronary perfusion. The secondary weakening of the beat is not usually observed in the natural circulation, the effect of coronary constriction being antagonised by the great rise of systemic blood pressure.

In 1908 Mummery and Symes published the results of some experiments on the blood pressure in animals while in a condition 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. They also report that the increase in blood pressure lasts from thirty to sixty times as long as that of the same amplitude from adrenalin. During the period of action a second injection is inactive or nearly so, but the first dose confers no immunity against adrenalin which when given after the pituitary effect has almost or quite passed
off, increases the arterial pressure to no less an ex-
tent and apparently for a longer time than it does in
the absence of a previous pituitary injection.

In its effects on the circulatory system it is
clear that pituitary extract is a stimulant of plain
muscle, that it must be carried in the blood stream
and produce its action by direct contact, and that in
the nature and distribution of its effects it has no
relation to innervation by the sympathetic system, the
pulmonary and coronary vessels being affected by it in
common with the arterioles of the system generally.
It has, however to be noted that in different organs
there is a varying amount of vaso-constriction. It
is relatively short in duration in the nasal mucous
membrane, more prolonged in the kidney and very persis-
tent in the case of the thyroid body. The cause of
this unequal distribution of effect is not known but
it cannot be due to inequalities of innervation by the
sympathetic system for the pituitary extract still re-
tains its selective action although the central ner-
vous system be destroyed. It may be due to the pre-
sence of some hormone or active substance in varying
quantities in the organs which it affects and with
which it must co-operate to produce its characteristic
action.
ACTION ON THE KIDNEY.

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

Dale conducted some experiments with the kidneys of dogs and cats. He first perfused them with oxygenated Ringer's Solution under constant pressure and then added pituitary extract to the circulating fluid, noting the rate of outflow before and after injection. He found that there was first a primary constriction of the vessels which was followed by a dilatation, but this primary construction was not comparable in extent to what takes place in the pulmonary and coronary arteries when similarly perfused. Houghton and Merrill obtained similar results. 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 kidney and diuresis, although their action when perfused through the isolated kidney is to cause constriction. It is possible that the reaction of the renal vessels to pituitary extract in their natural relations is a similar phenomenon to their reaction to the digitalis group of drugs.

From Dale's and Houghton's and Merrill's observations it would appear that the renal vessels are relatively insensitive to pituitary action. After an injection of the 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. This condition of general rise of blood pressure with dilatation of the renal vessels might possibly account for the diuresis produced by pituitary extract.

After an extensive use of all the pituitary extracts on the market, I have failed to find that diuresis is an invariable result of its administration. I have observed when an injection is given in midwifery cases that there is great diuresis at the beginning of the puerperium, but then, diuresis is a normal accompaniment of the condition. Nor, could the extracts I used be considered unreliable, for with them I obtained the
other characteristic effects of pituitary extract. In healthy young persons the results have usually been negative and never pronounced. In elderly men, on the other hand, administration was sometimes followed by a pronounced increase in the output of urine. Schiff showed by his experiments that there is a large increase in the total elimination of phosphoric acid when pituitary extract is administered to old men and as phosphoric acid excites the renal epithelium to secretion it is possible that in this manner the diuresis was produced in these cases. It has to be noted also 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 produced. It is scarcely probable that the renal vessels in man differ from those of other animals in being equally sensitive with the arterial system generally to the vasoconstrictor action of pituitary extracts but it is certain that the results of administration in practice do not correspond with those obtained experimentally.

Schafer attributed the diuretic effects which he obtained from pituitary administration to a second active principle, the increased flow of urine being due to the glandular cells of the organ being stimulated to activity by its agency. This hormone was described as being depressor in its action, and as evidence of
its existence, Schäfer and Herring found that while peptic digestion destroyed the action of pituitary extract on the blood pressure, it did not interfere with its diuretic action, whereas tryptic digestion left both actions unaffected. Dale's observations entirely disagreed with those of Schäfer and Herring. Using peptic and tryptic extracts of proved activity, he found that after twenty four hours of peptic digestion a pituitary extract had lost practically nothing of its pressor and diuretic properties, whereas after a few hours of pancreatic digestion both these actions had to all intents and purposes disappeared. Dale concluded that whatever destroyed one action destroyed the other. Further Schäfer and Herring laid stress on the fact that after a pituitary injection there is first constriction and then dilatation of the renal vessels and that if a repeated dose be given, which is inactive as far as a rise of blood pressure is concerned, marked increase in the rate of flow of urine can still be obtained. Dale points out that this is not an unusual phenomenon in cases where there can be no question of the presence of more than one active principle and instances strophanthus as an example. While not disputing the possibility of the existence of two principles, Dale considers that the pressor and diuretic effects of pituitary extract can be quite adequately attributed to one.
Houghton and Merrill\textsuperscript{42} have put forward the view that the diuretic effect is entirely secondary to the rise of blood pressure, and that administration of suprarenal extract produces a similar diuresis in consequence of the rise of blood pressure; but most observers are agreed that the latter substance produces a marked constriction of the renal vessels and cessation of the flow of urine.

**ACTION ON MUSCLE—UTERUS.**

It has already been stated that 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 that pituitary extract uniformly excites the uterus to tonic contractions in all species and in all conditions of functional activity. This latter fact was first demonstrated by Dale\textsuperscript{5} and later he ascertained that this action, like that on the arteries, is possessed only by the extracts of the infundibular lobe.

Cushny\textsuperscript{43} 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 injection into 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 gland on the uterus is simply further exemplification of what has been already stated, namely, 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, the arteries, the uterus, and the spleen being observed to be those most susceptible to its action. It is probable that the sarcoplasm of the heart is directly affected by the substance independently of the results brought about in it by constriction of the coronary arteries. It would appear to have no effect on voluntary muscle either directly or indirectly. It is essentially a stimulant of plain muscle.
VI. RELATIONSHIP OF THE PITUITARY GLAND TO OTHER DUCTLESS GLANDS.

Much has been learned recently regarding the role of 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. Where a rapid adaptation is required it is brought about by the nervous system, but when a slower action is required it is brought about by chemical influences. These chemical substances circulate in the blood-stream from one organ to another and bring about a correlation of the functions of the organs concerned. Formerly, these chemical substances were considered to be elaborated only by the ductless glands, but we know now that the thyroid, pituitary, thymus and suprarenal glands are not alone concerned in the production of these hormones, but that probably every tissue of the body takes part in their manufacture. If so, it follows that every cell plays some part in influencing the activity of the other cells. The subject is so complex that practically nothing is known of it. We know that an almost endless variety of chemical substances circulates in the blood, each of them of the vastest importance, but nearly all of them defying the most delicate methods of chemical research. The hormone of the medulla of
the suprarenal body has been synthesised in the laboratory and some light has been thrown on the physiological action of the hormones of the thyroid and pituitary glands by the removal in animals of the organ concerned. It cannot be doubted that further research will yield many valuable results, and that our knowledge of such diseases as exophthalmic goitre, Addison's Disease and acromegaly must be immeasurably increased by advances in our comprehension of the characters and functions of the hormones concerned.

It has been suggested that the thyroid, suprarenal, and pituitary glands supply the body with auto-protective substances. In health we enjoy immunity against poisons, whose elaboration within our organs is necessary to the activity of those or other organs. This immunity can only be conferred by the existence of internal antidotes and it is probable that the internal secretions supply these. They are dependent on each other, the one playing some part in determining the activity of the other. They maintain by their mutually reacting stimulus the good health of the body and they probably function as toxins and antitoxins to each other. When, however, there is an impairment of the balanced activity of opposed gland structures, one side gets the upper hand and there is consequently an excess of toxin produced, followed by a train of symptoms directly traceable to its effects. In exophthalm-
mic goitre there is excessive thyroid secretion. Good results have been obtained from the administration of both adrenalin and pituitary gland extract, results that cannot be entirely attributed to the effects these substances have on the cardio-vascular system. Enlargements of the pituitary and suprarenal glands have also been observed in this disease. It is probable that these three sets of glands form a group or part of a group of tissues mutually dependent on each other, and it is more than a mere surmise that the symptoms of exophthalmic goitre are due to impairment of their balanced activity. There is an excessive elaboration of a toxin on one side with relative deficiency of the normal antitoxin. The enlargement of the pituitary and suprarenal glands is probably in the nature of an effort to restore the balance and the good results obtained from administration of the extracts of these glands is probably because the antitoxin necessary to restore the balance has been supplied.

The fact that in myxoedema the pituitary gland hypertrophies would also seem to point to a relationship between that gland and the thyroid gland. It has already been pointed out that this enlargement cannot be of a compensatory nature. The physiological effects of their respective extracts seem to prove this, for thyroid extract produces no obvious result on the contractions of the heart, whereas pituitary extract
greatly increases their force; thyroid extract produces a fall of blood pressure but pituitary extract produces a great rise. The enlargement is more probably caused by toxic reaction and disturbance of interglandular equilibrium.

Several cases have been recorded in which symptoms of exophthalmic goitre have been replaced by those of myxoedema. The already enlarged pituitary gland in such cases would seem to pass on to a condition in which the elaboration of secretion is so excessive that it exceeds the amount necessary to balance the thyroid secretion and thus in turn becomes the toxin giving rise to the characteristic symptoms of exophthalmic goitre.

It would thus appear that there are good grounds for believing that there is a close relationship between the pituitary and thyroid glands. Evidence is not wanting that there is also a connection between the pituitary and the suprarenal glands. It has been pointed out that embryologically, histologically, and physiologically there are striking resemblances between them. It has been observed that pituitary administration produces hypersecretion of the pituitary gland itself, going on to diminished function if the doses are too large, or are administered for too long a period, diminished activity if too prolonged. It has also been observed that the pituitary body hypertroph-
ies after thyroidectomy or ablation of the suprarenal glands.

There is sufficient evidence to confirm the reciprocity of action of the thyroid, suprarenal and pituitary glands, and it cannot be doubted that the symptoms of Addison's Disease, exophthalmic goitre, myxœdema and other diseases are due in part at least to loss of interglandular balance and consequent toxaemia.

According to Sajous⁴⁴ the function of the suprarenal glands is to influence general oxidation and the temperature, besides stimulating metabolism and nutrition. The pituitary body, he states, is the governing centre for the suprarenals and he describes a direct nerve path between them. He also states that the pituitary is likewise connected with the thyroid and parathyroid glands by direct nerve paths, and that the thyroids and parathyroids enhance oxidation of all pathogenic elements in which phosphorus is present, besides sustaining metabolism and nutrition. The pituitary body in this way governs oxygenation, metabolism, and nutrition in all animals with thyroid and suprarenal glands.

We are familiar with the effects produced by administration of thyroid, suprarenal and pituitary gland extracts and with the results of the removal of these organs but their functions in the body remain obscure. We know that they assist metabolism and possibly furnish antitoxins but that is about all. There is every
reason for believing that there is a balanced activity of opposed gland structures but until a more complete knowledge of the nature of their functions is gained we can only conjecture as to their relationship to each other.
VII. CLINICAL RESULTS.

(1) Action on the heart and blood vessels.

In Section V. of this thesis it has been pointed out that different observers have proved that pituitary extract produces a rise in the blood pressure and that it is the infundibular portion of the gland that alone 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. With the other pressor principles just mentioned there is only a transient rise of blood pressure but pituitary extract with its much more prolonged action is capable of tiding the patient over the critical period of vaso-motor breakdown, a condition which saline infusions alone are incapable of affecting. Blair Bell has demonstrated its great value in this respect in cases of surgical shock.

It has been already mentioned that pituitary extract produces a prolonged constriction of the arterioles and increase of blood pressure, while its action on the heart is to strengthen the beat and to prolong
systole, thus considerably increasing the outflow of arterial blood from the left ventricle. In this way it follows that it must benefit venous congestion in cardiac failure by removing oedema and increasing the flow of urine.

In heart disease increasing importance will undoubtedly be attached to pituitary medication. Trerotoli found clinically that it effected a slowing and strengthening of the pulse as well as an increase of the blood pressure without noxious secondary effects. He found that irregular heart action becomes more regular. My own experience is that the extract is of great value in cardiac lesions with loss of compensation and in all cases of cardiac insufficiency with irregular and rapid action and low arterial tension. A stronger, more ample but slower pulse wave was invariably the result of such treatment, while irregularity became much less apparent. In such cases it has several decided advantages over digitalis; its action is almost instantaneous, it does not derange the alimentary system, and it is not cumulative but is probably as Dale has pointed out, excreted by the kidney unchanged.

In post-influenzal cardiac debility it has a remarkable effect in restoring tone to the cardiovascular system. In this condition I have frequently used it and always with the most gratifying results. The following case illustrates its value.
A man, aged 40 years, after going about for a few days suffering from influenza was put to bed and I was called in. When I first saw him he was in a sitting position, breathing quickly and with appearances of lividity. His pulse rate at the wrist was about 140, the pulse rate was irregular and very feeble. The heart was dilated, the impulse diffuse and felt well outside the nipple line. There was no murmur. The man had the appearance of dying. I gave him 1 cc. of Duncan & Co.'s Pituitary Extract. In 20 minutes his pulse rate was 120. It was quite regular and much stronger. Two hours after the injection the pulse had fallen to 110 and at the end of 12 hours the rate was still the same. Otherwise his condition showed remarkable improvement, the pulse was regular and fairly strong, the lividity had disappeared and the impulse was not nearly so diffused. At this stage I gave him another 1 cc. of the extract. At the end of 24 hours the pulse rate was about 90 and the cardio-vascular system seemed to have quite recovered its balance, there being no trace of dilatation. For the next three days I gave the patient 15 minims of the extract daily although I do not think this was necessary.

In other cases of acute dilatation of the heart, consequent on influenza, I have found pituitary extract restore the tone of the heart in an equally remarkable
way. In Section V., page 27 and 28 is given a record of the pulse and blood pressure of five cases. These injections were given to persons in normal health and in all, while the blood pressure returned to its normal level in two or three hours, the pulse rate was considerably longer in returning to the level at the time of the injection. I stated that this might be accounted for by the existence of a depressor as well as a pres¬
sor substance in the extract and that it is much more prolonged in its action than is the latter. The re-
markable effects of the extract in influenza can scarce¬
ly be explained in this way. After a single injection I have found the pulse rate become gradually reduced until at the end of 24 or 36 hours it was not much ab¬
ove the average rate of a normal pulse. It may be that the toxins of the influenza bacillus interfere with the proper secreting functions of the pituitary gland and that in this way, in part at least, the atonic con¬
dition of the cardio-vascular system is brought about.
The injection of pituitary extract into the blood stream besides having a direct stimulating effect on the heart and blood vessels may also probably stimulate the pituitary gland into a proper performance of its functions of supplying the amount of secretion neces¬
ary for the maintenance of the blood pressure at its normal level. Or, it may be that the pituitary ex-
tract injected, functions as an antitoxin to the toxins of the influenza bacillus and by neutralising them allows the pituitary secretion to regain its control as a regulator of the blood pressure.

In whatever way high blood pressure is brought about it eventually leads to degenerative changes in all the coats of the vessels. Étienne and Parisot proved that continued administration of pituitary extract results in cardiac hypertrophy and others have experimentally produced arterial degeneration by prolonged administration. In this respect it is like all other powerful pressor substances. It is essentially an emergency drug and as such has been proved to be of the utmost value in the treatment of collapse. Mummary states that for shock following the administration of anaesthetics it is likely to be "the drug of the future". Its use in cardiac disease should be confined to those conditions in which it is desired to raise the blood pressure and lessen the rate of the pulse. It should not be given when the blood pressure is high.

(2) Its employment in uterine conditions.

It has already been stated that pituitary extract produces powerful tonic contractions of the uterus in all states of functional activity. After normal labours 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 cases pituitary extract leaves nothing to be desired. The uterus almost immediately 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 minutes after injection---------------72.

II. Before injection------------------------118.
    10 minutes after injection---------------100.
    15 minutes after injection--------------80.

III. Before injection-----------------------120.
     10 minutes after injection--------------86.
     15 minutes after injection-------------76.

IV. Before injection------------------------110.
    10 minutes after injection--------------72.
    15 minutes after injection-------------60.

V. Before injection------------------------116.
   10 minutes after injection---------------92.
   15 minutes after injection-------------70.
VI. Before injection------------------100.
10 minutes after injection-------------82.
15 minutes after injection-------------60.

It is well known that immediately after delivery the pulse rate falls, but if this does not take place and the pulse rate remains at 100 or over there is a 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 case of that condition.

Mrs. M. 3-para. Aged 29 years.

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 cc. of pituitary extract intramuscu-
larly into the gluteal region and within 3 minutes a single strong uterine contraction expelled the child. The patient's other confinements were difficult instrumental cases and between the births of her first and third child only two years had elapsed.

This was obviously a case of fatigued uterine muscle. The pituitary extract stimulated its flagging energy and so hastened delivery. It can readily be understood that such a powerful ecbolic is absolutely contraindicated 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 perinaeum soft and yielding, although in repeated small doses it might probably be quite safely given.

The known action of the 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. C. Primipara. Aged 28.

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 cc. 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 exsanguine for a long time.

The other was a case of 'Accidental' Haemorrhage.

Mrs. C. 7th pregnancy.

At the end of the 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 Blockhart and 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.

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 these conditions I have used it with satisfactory results.

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

The uterus was enlarged. Menorrhagia was present, the menstrual flow lasting at each period for about ten 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 cc. of Duncan Flock-hart and Co.'s Pituitary Extract 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 of the extract and within twelve hours the menstrual discharge had entirely ceased, after having lasted a little over five days instead of ten as was commonly the case with her.

Every second day thereafter I injected \( \frac{1}{2} \) cc. of the extract until the next menstrual period when there was less dysmenorrhoea, and though I gave no injections 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 was entirely free from pain.
The patient had no tonics or douches. The treatment consisted entirely of ½ cc. injections of Pituitary Extract every second day for three months, Epsom Salts every second morning and regular exercise. Six months after beginning treatment the patient was enjoying normal good health, the endometritis being apparently quite cured.

In leucorrhoea and menorrhagia the results have been invariably good. In a series of cases of menorrhagia which had rendered the patients anaemic the pituitary extract reduced the period of flow to three or four days and restored the health in a remarkable way. The vaso-constrictor effect on the mucous membrane of the uterus and its striking tonic effects on the uterine muscle sufficiently explain the success of the treatment in these cases.

(3) Pituitary Extract as a diuretic.

Schäfer and Magnus discovered that an extract of the posterior lobe increased the flow of urine by reason of a vaso-dilator action of the vessels of the kidney. As I have already related in Section V, page 36 of this thesis, I failed in my cases to observe to any extent this diuretic property unless when I administered the extract to elderly men. In explanation of this I stated that Schiff proved that pituitary administration caused a large increase in the total elimination of phosphoric acid in old people and that as phosphoric acid has the property of stimulating the
renal epithelium to secretion it might be possible to attribute the diuresis in such cases to this cause. In this connection Marinesco's experiments in treating acromegaly with pituitary extract are interesting. The most distinctly pronounced phenomenon of the treatment was a marked diuresis. Schiff showed that pituitary extract, when administered in acromegaly, as in elderly men, resulted in a great increase of the total elimination of phosphoric acid. The diuresis thus obtained may possibly be due as in elderly men to the stimulating effect of the phosphoric acid on the renal epithelium. A condition of shock probably favours the diuretic action of the extract just as it serves to intensify its other properties.

(4) The action on intestinal muscle.

Blair Bell has pointed out that the extract is of great value in intestinal atony and paresis. He states that when there is no distention and when peristalsis is normally present an effect is not always observable. This is my own experience. In several of the cases for which I have employed it for other purposes there was a tendency to looseness of the bowels but generally there was no noticeable effect. In one case however I had an opportunity of confirming Blair Bell's observations on its value in such conditions. The patient was a lady, aged 54, who was suffering from cancer of the rectum and on whom a lumbar colotomy had been per-
formed. Great difficulty was experienced with the bowels and the various drugs tried gave only indifferent relief. On one occasion and without advice, she took four ounces of liquid extract of cascara with absolutely no result. Finally I gave her 1 cc. of Pituitrin and within five minutes there was a copious evacuation. In the treatment of atony and paresis of the intestines there thus seems to be a distinct promise that pituitary extract will prove to be a most valuable remedy.

(5) Other results.

(a) Exophthalmic goitre.

Renon describes a case of exophthalmic goitre in which three weeks treatment with Pituitary Extract brought about reduction of the goitre, of tachycardia, exophthalmic tremor and perspiration. There was also a decrease of the congestion spreading towards the head, and a great improvement of the digestive troubles and of the condition generally. Parisot was equally successful with his cases.

I have treated one case of exophthalmic goitre with pituitary extract and with very encouraging results. My patient was a young woman of 25 years of age, and had suffered from this disease for a considerable number of years. After coming under my care I treated her with potassium iodide and strophanthus and she certainly derived benefit from these drugs, but in August 1910, I began the administration of pituitary ex-
tract. The preparation I first used was Pituitrin of which I injected 1 cc. intramuscularly every second day. The usual fall of the pulse rate and increase of blood pressure took place but a remarkable fact was that the effect on the pulse rate was very prolonged. Before each successive injection it was slower than before the previous injection. Before the first injection it was 140; before the second 120; before the third 106; before the fourth 102; before the fifth 98, and before the sixth 92.

After one week of treatment the patient said she had not felt so well for years and that, whereas, before, she was much troubled with sweating, that symptom had quite disappeared and that she slept well and soundly in contrast with the insomnia from which condition she previously suffered. Before the pituitary treatment was commenced palpitation was the chief symptom of which she complained, but this had also improved much at the end of a week. After three weeks the patient no longer complained of tremor, she was much less excitable, the tendency to flushings of the face and neck had greatly decreased, there was no longer the constant thirst nor the craving for unusual articles of food from which she formerly suffered. At this period there was no appreciable diminution of the goitre nor of the exophthalmos.

I now stopped the injections and gave the patient
Burroughs, Welcome & Co.'s tabloids of the whole gland, one, thrice daily. They answered apparently equally as well as the infundibular extract, the improvement already secured being maintained. After four months treatment the condition of the patient was remarkable. She had put on flesh considerably, there was a great accession of strength, the goitre was distinctly less and there was very marked improvement in the exophthalmos. Menstruation which before was irregular and excessive had become perfectly normal and the leucorrhoea from which she had suffered was cured. From that time up to the present the patient has taken only two tabloids once daily and there has been no relapse.

In accounting for the results in this case one is almost compelled to believe that the antitoxin theory is the correct solution. It has been shown that in exophthalmic goitre there is increased secretory activity of the thyroid gland and it has been inferred that the excess of secretion is the cause of the symptoms. A comparison of the symptoms of exophthalmic goitre with those of myxoedema presents many points of contrast. The myxodematosus patient gets stouter, the other loses flesh, the one is intolerant of cold, the other of heat, the skin of one is dry, of the other moist, one is slow and deliberate, the other irritable and excitable. The heart's action in one is quiet and in the other rapid. Furthermore, we know that by administration of large
doses of thyroid extract we can produce many of the symptoms of exophthalmic goitre, such as increased rate of the heart's action, loss of body weight and sweating. It is very probable that the secretion of the pituitary and thyroid glands, in health function as toxins and antitoxins and that in exophthalmic goitre there is an impairment of that balanced activity. The thyroid gets the upper hand and there is an excessive and one-sided elaboration of a toxin whose normal antidote, the pituitary secretion, is relatively deficient and the whole train of symptoms is directly traceable to this toxin. By the administration of pituitary extract we probably supply the natural antitoxin and thus restore the balanced activity of these opposed gland structures. It appears more than a surmise to account in this way for the very marked improvement I obtained in the treatment of this case of exophthalmic goitre.

(b) Skin diseases.

It has been suggested that in certain skin diseases such as dermatitis, urticaria, and acne, pituitary extract might be of value. I have employed it in acne vulgaris very successfully.

The patient was a young unmarried woman aged 24 years.

The face was much disfigured. Menstruation was irregular both as to time and quantity. Her pulse was
quick and irregular. Among the remedies tried were iron, potassium permanganate, arsenic and vaccine treatment, and all without success. She was always much improved after a menstrual period if there had been an abundant discharge.

I prescribed 15 minims of Duncan Flockhart & Co.'s Extract thrice daily and very soon a decided improvement manifested itself, resulting in at least a temporary cure. Menstruation became regular and the pulse slower and quite regular.

The disturbing agency here causing a departure from the balance of health was probably of a hyperaemic nature. The pituitary extract by producing a more active peristalsis of the muscular fibres of the uterus would have an emmenagogue effect and thus relieve the condition.

(c) In asthma.

Pituitary extract has proved extremely beneficial in the treatment of asthma. I have used it frequently in this disease and always found it act in a marvellous manner and to have a more enduring effect than adrenalin. If the cause of the obstruction of the tubes is hyperaemia of the vessels it can readily be understood why Pituitary Extract with its vaso-constrictor action should relieve the condition, but, if, as is more generally believed, there is a spasm of the muscles, the explanation of its action is probably that by raising the blood pressure and increasing the outflow of art-
eral blood from the left ventricle it possibly raises the tonus of the medullary centres.

Pituitary extract has been recommended for other conditions than those I have detailed. It has been used in typhoid fever, tuberculosis and paralysis agitans. Sufficient evidence has also been brought forth to warrant a trial of this substance in certain conditions of mental and physical backwardness.

So far I have demonstrated that in my practice pituitary extract has been a more or less successful remedy for various pathological conditions. I have been careful to select cases in which good results might be expected taking as my guides the physiological action of the drug so far as it is known and the experience of others. In the majority of my trials I thus met with some success but in others I was unsuccessful. I have already mentioned that its diuretic properties have not manifested themselves to any great extent in my experience. In two cases of cardiac disease with low blood pressure, much dropsy, and scanty urine, I administered it unsuccessfully so far as the production of diuresis was concerned. In a case of Bright's Disease with general anasarca following an attack of septicaemia I was also unsuccessful in increasing the flow of urine with pituitary extract whereas diuretin produced a very abundant discharge. In epilepsy I found no benefit from its administration and in a case of arterio scler-
osis it produced intense headache. Some observers state that they have got good results in the latter disease. In my opinion it is absolutely contraindicated.

I have employed it in only two cases of skin disease—acne vulgaris and psoriasis. Its effect on the former as already stated was very satisfactory but the psoriasis derived no benefit from it.

Dosage and method of using.

The extracts I have used are Park Davis & Co.'s Pituitrin, Duncan, Flockhart & Co.'s Pituitary Fluid and Burroughs, Welcome & Co.'s Pituitary Extract and also the latter firm's tabletts of the whole gland.

To secure rapidity of action the best mode of administration is by intramuscular injection either into the deltoid region, into the supinator group or in the gluteal region. When given by the mouth it is but slowly absorbed but nevertheless produces its characteristic results.

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 cc. to 1 cc. hypodermically and up to 1.5 cc. 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 administrations of pituitary extract are 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.
VIII. SUMMARY AND CONCLUSIONS.

Whereas the majority of observers have found extracts of the anterior lobe of the pituitary body to be inactive, clinical and experimental work have shown that extracts of the infundibular lobe possess very active properties.

I. 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 administration. The decrease in the pulse rate continues much longer, for twelve hours or even more. Irregular heart action becomes more regular.

The extract is of great value in cardiac lesions with loss of compensation, and in all cases of cardiac insufficiency with irregular and rapid action and low arterial tension.

In post-influenzal cardiac debility it is particularly effective in restoring tone to the cardio-vascular system and would seem in a striking manner to counteract the toxaemia.

It is probably the most valuable agent we possess for the treatment of shock after operations or anaesthetics.

II. The action of the extract on the uterus is to
produce powerful tonic contractions. In this respect its effects are more rapid and persistent than those of ergot preparations.

After normal labours it is of value as a prophylactic against haemorrhage and as a means of lessening after pains.

In the absence of all obstacles to rapid delivery it is of great service in uterine inertia.

It is highly efficient in controlling post-partum haemorrhage and in the treatment of menorrhagia and leucorrhoea.

It is a valuable remedy for Endometritis.

III. As a diuretic its precise value is uncertain. Different observers have shown that when administered to anaesthetised animals a very marked flow of urine follows. The results in clinical practice do not correspond with those obtained experimentally. A condition of shock would probably favour the diuretic action of the extract just as it serves to intensify its other properties.

IV. Pituitary extract is essentially a stimulant of plain muscle and in this respect is likely to prove a reliable remedy in conditions of paresis and atony of the intestines particularly after operation.

V. There is good reason for believing that the infundibular extract is antidotal to excessive thyroid action. In exophthalmic goitre which is believed to
be the result of excessive thyroid secretion pituitary extract brings about a remarkable improvement in the symptoms. It probably does so by supplying the natural antitoxin and thus restoring the balanced activity of the opposed gland structures.

VI. In certain skin diseases such as acne vulgaris, it is of value. On psoriasis it seems to have no curative effect. It is probably those skin diseases depending on a hyperaemic condition which will derive benefit from its administration.

VII. On asthma and hay fever its effect is sometimes nothing short of marvellous probably because of a raising of the tonus of the medullary centres.

VIII. Pituitary extract should not be given in conditions of high blood pressure nor should its administration be too long continued, as cardiac hypertrophy and arterial degeneration may be produced.

There is much difficulty in interpreting the results, the whole matter being yet in an experimental stage but the success already achieved gives great promise that in pituitary extract we have a remedy which will finally be of great importance to mankind.
IX. BIBLIOGRAPHY.


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