RECENT ADVANCES IN HORMONE THERAPY.*

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INTRODUCTION.

Within recent years much experimental work has been carried out on endocrine problems and has added considerably to our knowledge of the physiology of the endocrine system, but the therapeutic application of this knowledge is still in its infancy. This is due partly to the fact that it is only recently that sufficiently pure and concentrated extracts have been produced for human administration, and partly to the fact that the expense of these products often prevents their extensive use. Extracts have also been obtained which so far appear to have little clinical application, but with the advance of knowledge there is no doubt that they will find a place in the treatment of certain conditions.

Before briefly surveying the use of various hormones in treatment, it will not be out of place if a few words be said about the physiology of the anterior pituitary, as there is no doubt that this organ, small though it be, plays an important part in governing the development and function of the rest of the endocrine system. It is well-known that removal of the pituitary in experimental animals leads to atrophy of the endocrine glands, with disturbances in the organism as a whole consequent on the lack of specific secretion of each individual gland. Clinically this is well-shown in the rare condition of Simmonds' disease, the symptoms of which are caused by destruction of the anterior lobe of the pituitary by a tumour or embolus, or by simple atrophy. In this malady the chief features are profound cachexia, mental changes, loss of the hair and teeth, atrophy of the testes, prostate and seminal vesicles, amenorrhœa and atrophy of the uterus and ovaries, a low blood pressure probably due to atrophy of the suprarenals, low basal metabolic rate, anæmia and hypoglycæmia. The deficiencies resulting from removal of the pituitary in the laboratory animal are almost completely repaired by the implantation of fresh anterior pituitary tissue.

From the widespread changes produced by the removal or destruction of the anterior pituitary one is little surprised at the numerous extracts with different properties that have been prepared from this organ. It is not in the scope of this lecture to give an account of the actions of all these factors. Suffice it to say that at the present time it is considered that the anterior pituitary hormones consist of the following:—

1. *Growth hormone.*
2. *Gonadotropic hormones*, including
 - (a) the ovarian follicle and male germ cell stimulating hormone,
 - (b) the luteinising hormone, which also stimulates the interstitial tissue of the testes.
3. *Thyrotropic hormone*, which stimulates the thyroid to produce an increased amount of its iodine containing hormone.
4. *Adrenotropic hormone*, through which is stimulated the cortex of the suprarenals.

*A Post-graduate Lecture delivered at St. Bartholomew's Hospital on June 20th, 1936.

5. *Parathyrotropic hormone.*
6. *Metabolism or diabetogenic hormone*, which consists of a blood sugar raising principle and a ketogenic principle.
7. *Pancreatotropic hormone*, which depresses the level of the blood sugar and depletes the liver glycogen. It has no effect after removal of the pancreas.
8. *Lactogenic hormone* (prolactin), which excites milk secretion in the fully developed mammary gland.

It is remarkable that so small an organ can elaborate so many substances with such widely different functions. Zondek has suggested that they are derived from a basic substance by comparatively insignificant changes in its molecule, and if one takes as an analogy the close chemical relationship between oestrin and the male sex hormone, I imagine that this view is not far from the truth.

HORMONE THERAPY.

The use of endocrine preparations gives more scope to the quack than almost any other branch of therapeutics, and in the daily armful of circulars which one receives claims are made which have no clinical proof or scientific basis whatsoever. This is disturbing to the practitioner who, for lack of time, is unable to delve into the welter of published papers which are ever increasing. My remarks will be confined mainly to the use of preparations in conditions in which I have had personal experience, and for this reason I will say little of their value in gynaecological states.

Anterior Pituitary Hormones.

Of the anterior pituitary hormones that have been enumerated three are available for clinical use—the growth hormone, the gonadotropic hormone and the thyrotropic hormone. As yet they are expensive, and little work has been done to demonstrate their full value in clinical medicine.

Growth Hormone. There have been reported, mainly in the United States, cases of pituitary infantilism in which increased growth has been obtained by the injection of 1 c.c of growth hormone three times weekly for several months. The earlier such treatment is instituted the better is the response, the most favourable results being in cases in which there is a delay in osseous development and epiphyseal closure. Once epiphyseal closure has occurred, further stimulation of statural growth is prevented. It has been found that growth hormone in conjunction with thyroid gives better results than growth hormone alone. I have had no experience, however, with this hormone. At the present time there is no method for its standardisation and one is never sure of its activity. Further, it is well-known that cases of infantilism may occasionally have spurts of spontaneous growth.

Gonadotropic Hormone. From work on laboratory animals it has been found that the gonadotropic hormones of the anterior pituitary consist of two main factors. One factor, (prolan A), in the female brings about maturation of the Graafian follicle, and as a result the production of oestrin, which acts on the uterus; in the male it stimulates spermatogenesis. The other factor (prolan B) in the female converts the follicles into corpora lutea, imprisoning the ova, inhibits the production of oestrin and stimulates the production of progesterin, the hormone formed by

the corpus luteum. In the male this luteinising factor stimulates the interstitial tissue of the testes, so that this hypertrophies and produces increased amounts of the male sex hormone. This in turn increases the size of the penis and scrotum, and causes enlargement of the seminal vesicles and prostate by acting on their fibro-muscular stroma and glandular elements.

In pregnant women gonadotropic hormones resembling in action those of the anterior pituitary are excreted in large quantities in the urine. Being more easily obtained, they are cheaper than those extracted from the anterior pituitary and are consequently more widely used. They are not, however, identical with the anterior pituitary gonadotropic hormones and are probably placental in origin. Pregnancy urine extracts contain larger quantities of prolan B than of prolan A; consequently when they are injected into laboratory animals the action of prolan B predominates, in that marked luteinisation is produced in the ovary in the female and hypertrophy of the interstitial tissue of the testes in the male. There is little or no effect on spermatogenesis. Of the various commercial preparations may be mentioned prolan, pregnyl, antuitrin S., gonan and follutein.

Undescended testes. It has been shown that daily injections of pregnancy urine extract containing gonadotropic hormones bring about descent of the testes in 14 days in the immature monkey, in which animal they are normally situated in the inguinal canals. The gonadotropic hormones of pregnancy urine have been applied to the treatment of undescended testes in man. In collaboration with Dr. E. F. Scowen, I have used them extensively in this condition. Before considering treatment, care should be exercised in determining (1) the situation of the testis—if the testis be ectopic, i.e., lying outside the inguinal canal, descent of the organ cannot be brought about by hormone therapy—and (2) whether the testis can be brought into the scrotum by manual pressure—if it can, it is extremely likely that the testis will descend spontaneously before or at puberty. In this type of case, however, the administration of prolan will speed its descent.

The ages of our early patients ranged from 4 to 26 years. The dose of hormone recommended by us is 500 rat units given twice weekly intramuscularly; in obstinate cases it is our practice to give the injections for three months alternated by three-monthly rest periods, as there is experimental evidence that the organism acquires a resistance to the hormone after prolonged administration. Descent of one or both testes occurred in 75 per cent. of our bilateral and in 60 per cent. of our unilateral cases. The duration of treatment varied from 3 weeks to 14 months.

There are no alarming reactions as a result of the treatment. After the first, and occasionally after the second, injection, there may be local pain and swelling. In rare cases after the first injection there may be a general reaction consisting of malaise, anorexia, nausea and headache. Inguinal hernia is frequently associated with an undescended testis, and in some cases a hernia becomes obvious during treatment. It is probable that the hernia was present from the beginning, and only became noticeable as the testis descended, the hernial sac presumably descending with the testis. In such cases the hernia should be cured by radical operation. During treatment there is usually some enlargement of the penis and testes and growth of pubic hair.

If treatment is started when the patient is very young, precocious sexual development may occur. If however it is delayed till puberty in the hope of spontaneous descent, degenerative changes may take place in the testis. It is wise therefore to begin treatment between the ages of 10 and 13 years.

Azoospermia. There is no doubt that in an animal, in which the testes have atrophied as a result of removal of the pituitary, the daily injection of gonadotropic extract from the anterior pituitary will stimulate spermatogenesis. Whether pregnancy urine extract will bring about the same effect is controversial. There have appeared one or two reports of cases of sterility in man due to deficient spermatogenesis which have been successfully treated with urinary gonadotropic hormones. In view of the experimental findings, however, that anterior pituitary extracts are far more effective than urinary extracts in stimulating spermatogenesis in the hypophysectomized animal, they are more likely to prove successful in the treatment of azoospermia in man.

While dealing with the question of sterility in the male, it should be remembered that a considerable percentage of patients with definite hypothyroidism are sterile, and that adequate thyroid secretion is essential for the normal function of the gonads. In the investigation of a case of sterility the thyroid factor should be taken into consideration, for the administration of thyroid is occasionally of great value.

Obesity. In obesity of the so-called "pituitary type" pituitary and urinary gonadotropic hormones have no effect in reducing the weight or amount of fat. This agrees with the experience of most observers. The most effective means at present known of treating obesity is to reduce the intake of food, with or without thyroid medication.

Functional Uterine hæmorrhage. Concerning the treatment of this condition I am not entitled to speak, as I have had no personal experience. It appears to be the experience of gynæcologists that the injection of urinary gonadotropic hormones in doses of 100 to 500 rat units daily results in an immediate or early relief of symptoms. The injection of corpus luteum hormone (syn: progestin, proluton, corporin) brings about the same effect. One may justifiably conclude that proluton causes cessation of bleeding by stimulating corpus luteum formation. This however appears to be incorrect. There is no evidence of a corpus luteum effect on the endometrium after the bleeding has stopped, and it is considered that proluton rapidly diminishes the secretion of œstrin by causing regression of the ovarian follicles.

Thyrotropic Hormone. As far as one can tell at present, the clinical application of this hormone is extremely limited. In cretinism and myxoedema, in which the thyroid gland is exhausted or atrophic, thyrotropic hormone has little or no effect (Scowen)—a state of affairs which, considering the pathology of these diseases, one would logically expect. In other conditions, e.g. obesity, results can be obtained more cheaply and as effectively by dried thyroid substance.

In the rare condition of Simmonds' disease, in which the thyroid gland is inactive through lack of stimulation by the anterior pituitary, the thyrotropic hormone has its uses. The rational procedure in the treatment of this disease is to supply the pituitary hormones in which the organism is deficient. Preparations are now on the market containing 150 units of thyrotropic hormone and 50 units of anterior pituitary gonadotropic hormone per c.c. The dose required will depend on the severity of the disease. Because of suprarenal atrophy cortin may also be necessary in initial daily doses of 5-10 c.c. intramuscularly.

Thyroid.

The uses of thyroid hormone are well known and do not require enumeration here. I would remind you that in the treatment of simple goitre, thyroid is far more effective than iodine. The rationale of treatment is to rest the thyroid as completely as possible in order to cause atrophy of some of the epithelial elements. In a simple hyperplastic goitre, in which there is considerable hyperæmia, iodine reduces the size of the gland by causing disappearance of the hyperæmia during involution to the colloid state. The gland, however, has still to manufacture thyroid hormone, so that there will be little further diminution in its size. The most effective means of ensuring as complete rest to the thyroid as possible is to give dried thyroid substance. The mistake is frequently made of not giving sufficiently large doses. It is said that the daily dose of dried thyroid that should be given to a completely thyroidless individual to maintain a normal basal metabolic rate is about 5 grains. Therefore in order completely to rest the thyroid in a patient with simple goitre one should try to give at least 5 grains per day, a careful watch being kept on the weight, pulse rate and general condition. The best plan is to start with doses of 1 grain twice daily and gradually increase to the patient's tolerance. It is obvious that in old standing nodular and colloid goitres with much fibrosis, cystic degeneration or calcification, little or no reduction in size can be obtained by medical means.

Parathyroids.

The chief therapeutic value of parathyroid extract (syn: parathormone) is dependent on its action in raising the level of the blood calcium. Its major use therefore lies in the treatment of acute tetany following accidental removal of the parathyroids during thyroidectomy. Large doses may be required—40-100 units per day subcutaneously; it is advisable to give in addition calcium chloride 30 grains three times daily by mouth. The immediate relief of tetanic symptoms however may be obtained just as effectively and more rapidly by the intravenous administration of 50 c.c. of a 4 per cent. solution of calcium chloride; care should be taken that it be given slowly and that none enters the subcutaneous tissues, as necrosis and ulceration may result. To avoid such a complication, 10 c.c. of a 20 per cent. solution of calcium gluconate may be given instead of calcium chloride. In the treatment of chronic tetany, parathormone may be dispensed with, a cheaper and equally effective method being the administration of 30 grains of calcium lactate and 30 minims of radiostol three times daily.

Parathormone has been recommended for ulcerative colitis, given in 20 unit doses on alternative days in conjunction with 60 grains of calcium gluconate three times daily. It is sometimes useful in relieving the abdominal pains associated with intestinal spasm in this condition.

Suprarenal Cortex.

The use of suprarenal cortical hormone (syn: cortin) in the treatment of Addison's disease is now well known, and since the discovery that there is an increased excretion of sodium associated with a low blood sodium in this condition the administration of sodium chloride in doses of 10-20 grams per day has considerably reduced the amount of cortin which these patients require (Graham). In fact in mild cases treatment with salt may even render the administration of cortin unnecessary. In severer cases, however, patients always feel much better when receiving cortin in addition to salt, and often the administration

of cortin is absolutely essential. In crises 50 c.c of cortin should be given intravenously together with glucose saline. The maintenance dose required will vary in each case from 5-20 c.c. daily.

Cortin is also of use in the treatment of shock. After severe infections, such as diphtheria, pneumonia and influenza, in which there may be some cortical damage, cortin may be of service in treating the asthenia which persists during convalescence. It is also suggested that it is useful in infantile marasmus, a statement which requires further investigation. I have seen no benefit following its administration in toxic goitre.

Ovaries.

Female Sex Hormone (œstrin). The proprietary preparations of this hormone are known as theelin, menformon, œstroform, progynon, folliculin and amniotin; more potent and more soluble preparations are known as dimenformon, œstroform B and progynon-B oleosum. The treatment of gynæcological conditions, such as primary amenorrhœa, in which œstrin is of value, is in the province of the gynæcologist rather than the general physician and will not be dealt with in this lecture. I have found œstrin of value in the treatment of menopausal conditions in doses of 1,000-10,000 international units daily by mouth. Owing to its action on the vaginal epithelium, it has recently been used for vulvo-vaginitis of children—gonococcal and non-gonococcal. For this condition the doses suggested are 4,000-5,000 international units daily by mouth or 1,000-2,000 units daily subcutaneously for periods varying from 1 to 3 months. Usually the discharge clears up after 3 or 4 weeks' treatment. Should relapses occur, the treatment should be repeated, or a single large dose of 50,000 international units may be given intramuscularly.

œstrin causes no improvement in toxic goitre, even when given in very large doses such as 50,000 units intramuscularly for 3 weeks. It is said to lower the blood pressure in essential hypertension, to make the hair grow in alopecia and to make the hair fall out in those who have a superabundance, but all my attempts with the hormone in these conditions have resulted in failure.