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ON

THE EXPERIMENTAL BASIS OF ENDOCRINE THERAPY.*

BY

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THE laboratory worker and the clinician naturally regard therapeutic measures from a slightly different angle, since the former is concerned chiefly to know what facts can be considered as fully proved, and the latter wishes to know what measures offer a fair chance of benefiting patients. The history of therapeutics teaches us, however, with no uncertain voice, that once speculation and imagination get free from the restraint of rigidly controlled observation there is no limit to the distance which they may wander from the paths of truth. Complex systems of treatment based on inaccurate deductions have repeatedly been built up, and have been almost universally accepted and followed until some advance of knowledge, or even some change in fashion, has sufficed to upset the whole system, and the treatment has been universally discarded and often has come to be regarded as not only useless but actually harmful.

When considering any system of treatment it is very necessary to distinguish clearly between that part of it which is definitely proved and that part which is based merely on plausible deductions, and in no case is this attitude more essential than when considering the recent developments of endocrine therapy.

The discovery of the function of the organs of internal secretion opened up a whole new field of physiology, and this knowledge led to brilliant and dramatic successes in the treatment of thyroid deficiency. This initial success suggested boundless possibilities in the use of organ extracts, and endocrine therapy has gone forward on the assumption that extracts of every other organ of internal secretion ought to yield results comparable to those obtained from thyroid therapy. There has been every temptation for therapeutic practice to outrun scientific fact, and in addition commercial enterprise has certainly done its full share in assisting in the development of endocrine therapy. The result is that endocrine therapy is coming to bear a suspicious resemblance to mediaeval magic; the savage believes that eating the heart of his enemy will confer on him the virtues of this enemy, and the more enthusiastic vendors of endocrine remedies suggest that the consumption of extracts of practically any organ will cure diseases of that organ. The general line of thought and the extent of scientific foundation are about the same in both cases.

These considerations indicate how essential it is in the case of endocrine therapy to examine the evidence closely and distinguish clearly between the remedies whose use is based upon definite evidence, and those whose use is simply based on inference. The subject of endocrine therapy can be divided into two fairly distinct divisions: (1) substitution therapy—that is, the administration of the extract of an organ in order to compensate for the deficient secretion of the organ; and (2) the use of extracts of tissues as pharmacological agents, when there is no question of substitution for a deficient secretion.

The use of adrenaline as a vaso-constrictor and the use of pituitary extract as an oxytocic are examples of the second class of action. In these two particular cases extracts of endocrine organs are used, but active pharmacological agents can also be obtained from other kinds of tissues. For example, Abel and Macht¹ found that the poison gland of

the toad, *Bufo aqua*, contained 6 per cent. of adrenaline and also bufotoxin, the latter being a digitalis-like substance which produced the same therapeutic action as digitalis. This example is interesting because it shows how erroneous it is to assume that, because a tissue contains a specific substance with interesting and powerful pharmacological actions, therefore this agent must be an internal secretion.

Substitution Therapy.

Substitution therapy is the most important division of endocrine therapy, and it is advisable to consider the postulates that should be fulfilled before we can assume that an organ extract acts in this way. Gley² has laid down three conditions which should be fulfilled before it is assumed that an organ produces an internal secretion.

1. The histological condition. The organ must contain secretory cells in intimate relation with the blood vessels and without any duct for external secretion.
2. The chemical condition. A specific chemical substance must be identified both in the organ and also in either the venous blood or lymph coming from the organ.
3. The physiological condition. The venous blood or lymph coming from the organ must produce the pharmacological actions produced by the specific substance.

Gley³ has recognized that these conditions are so severe that they would rule out most of the endocrine organs, and has suggested that in default of the above conditions two other concurrent tests may be accepted—namely, (1) the destruction of the gland produces deficiency symptoms which present a clearly defined syndrome; and (2) this syndrome is relieved by grafting of the gland or by administration of organ extracts.

These tests of Gley's are framed to test the physiological actions of organs, but from the point of view of pharmacology slightly different tests are required. For example, even if grafting of a gland produces benefit in a deficiency syndrome, it does not follow that the administration of organ extracts will be successful.

Endocrine therapy may be considered to rest on a solid scientific foundation when the following conditions are fulfilled: (1) The destruction of a gland produces a characteristic syndrome. (2) The administration of extracts of the organ relieves this syndrome. (3) Some chemical or pharmacological test exists by which the activity of the extract can be recognized and if possible be measured. It is important to realize that even if the first condition is fulfilled it does not follow that the second condition will also be fulfilled.

An endocrine organ may fail to produce an active extract for several reasons. (1) The action of the gland may be in part or entirely a detoxicating action, in which case the administration of gland extracts will have no effect. (2) The gland may secrete its internal secretion as rapidly as it is formed. In such a case the gland will contain no store of internal secretion and its extracts will be inert. (3) The active principle may be so labile that it cannot be isolated.

In any of the above three cases grafting of the gland may be expected to relieve deficiency symptoms, but administration of gland extracts will produce no effect. All the known hormones are relatively unstable bodies, although some are much more unstable than others, and it is interesting to consider that Minchowski, as early as 1889, showed that removal of the pancreas produced diabetes, but it was more than thirty years before anyone succeeded in isolating the active principle of the pancreas in a stable form. Another difficulty is that it is necessary to discover the correct method of administering organ extracts, for in many, if not most, cases these are destroyed in the gut before absorption.

These considerations show how wide is the step between proving the effects produced by deprivation of an internal secretion and the discovery of the correct method of isolating and administering an extract to cure this deficiency. Unless some test exists by which the activity of an organ extract can be recognized these difficulties are almost insuperable.

So-called endocrine remedies have been prepared from every tissue of the body, but it is only necessary to consider those organs which fulfil the first condition—namely, that

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their deprivation produces a definite syndrome suggestive of deficiency disease. Such glands are nine in number.

Gland.	Chief Effects produced by Destruction or Deficiency of Gland.
1. The thyroid	Cretinism or myxoedema.
2. The parathyroids	Tetany, and derangement of calcium metabolism.
3. The islet tissue of the pancreas	Inability of tissues to utilize carbohydrates; hyperglycaemia and glycosuria.
4. The testicles	Eunuchism.
5. The ovaries	Premature menopause.
6. The suprarenal cortex ...	Asthenia, low blood pressure, and death in a few days.
7. The suprarenal medulla	The effects produced are doubtful.
8. The anterior lobe of the pituitary	Infantilism and obesity.
9. Posterior lobe of the pituitary	Increased carbohydrate tolerance. Diabetes insipidus (P).

Unfortunately only a few of these glands fulfil the second condition in at all a satisfactory manner. The evidence regarding the different glands is shortly as follows.

The Thyroid.

The evidence for substitution therapy in the case of the thyroid is practically complete. Administration of dried thyroid relieves the symptoms of thyroid deficiency, the active principle thyroxin has a known chemical formula and structure, and the activity of thyroid preparations can be estimated by physiological tests. Finally, it is known that thyroid extract produces its specific action when given by the mouth. In addition, hypertrophy of the thyroid produces a definite syndrome, and many of the signs of this syndrome can be produced by administering excess of thyroid gland.

The Parathyroids.

Unfortunately there is doubt whether the tetany produced by extirpation of the parathyroids can be relieved by administration of parathyroid. Biedl, for example, obtained consistently negative results in such experiments performed on cats.

The parathyroids are believed to have a double action—a detoxicating action consisting in the destruction of guanidine compounds, and a second action on calcium metabolism.

Vines⁴ has reported valuable results from the administration of dried parathyroid in chronic sepsis. The preparation caused a rise in the calcium in the blood and a rapid clinical improvement. This action, however, is not of necessity an example of substitution therapy.

The Islet Tissue of the Pancreas.

As has already been mentioned, the connexion between the pancreas and carbohydrate metabolism has been known for more than thirty years, but the difficulty of extracting the active principle from the pancreas has only recently been overcome by the work of Banting and Macleod. Apparently the internal secretion of the pancreas can be temporarily replaced by the injection of insulin, and the use of insulin is a true case of substitution therapy.

It is instructive, however, to compare the difficulties attending the isolation and administration of insulin with the administration of thyroid. Dried thyroid given by the mouth is an effective means of substitution therapy in the one case, but in the case of insulin the discovery of a method for the extraction of the active principle was a matter of great difficulty, and even now when a suitable method has been discovered it is necessary to test every batch manufactured, since any small error in extraction will result in an inactive product; moreover, insulin has to be given hypodermically, for it is inactive when given by the mouth or when sprayed into the nose.

The Gonads.

The effects of castration or spaying have been known for centuries, and there is satisfactory evidence that many of these effects can be relieved by grafting of glands. The evidence as to the effect of testicular and ovarian extracts is, however, extremely unsatisfactory. Every imaginable claim has been made as to the action of these extracts, but all the more careful observers are very reserved in their opinions. Professor Murray⁵ recently stated:

"There is very little satisfactory evidence that either testicular or ovarian preparations have any therapeutic action when injected

or taken by the mouth. The development of eunuchism after removal of the testicles and the corresponding condition after removal of the ovaries are generally considered to be due to loss of internal secretion of the gonads. There is, however, no evidence that either eunuchism can be removed by the use of testicular extract or the signs of a premature post-operative menopause averted by taking ovarian tablets. The relief of subjective sensations has been reported, but this is not sufficient evidence."

The use of testicular extract was, of course, the first example of attempted substitution therapy, for it was introduced by Brown-Séquard in 1889. There is, however, to-day no satisfactory evidence that we have yet succeeded in obtaining a preparation from either the testicles or the ovaries which will produce a true substitution effect.

The Suprarenal Cortex and Medulla.

These conjoined glands present a remarkable and even paradoxical contrast as regards endocrine therapy.

We know that the suprarenal cortex is absolutely essential to life and that its destruction rapidly causes death. Nevertheless, we do not know for certain whether the cortex acts as an organ of internal secretion, or whether it has only a detoxicating action, and no one has obtained from it an active extract.

On the other hand, the suprarenal medulla contains the intensely active substance adrenaline. The chemistry and pharmacology of adrenaline have been fully worked out, and it is possible to make fairly accurate quantitative estimations of the adrenaline content of the medulla. We know, however, very little indeed as to the physiological action of adrenaline. Recent work makes it doubtful if the destruction of the suprarenal medulla produces any very definite effects, and Cannon,⁶ in a recent paper, concluded:

"There is no satisfactory evidence that, in natural quiet existence, the suprarenal medulla gives off any secretion whatever. In times of stress it is brought into action by nerve impulses, and may then support the influence of the sympathetic system and have besides special functions of its own."

The evidence for successful substitution therapy in the case of either the suprarenal cortex or medulla is therefore very scanty. In Addison's disease there is destruction of both the cortex and medulla, but extracts of the suprarenals do not cure this condition, although adrenaline may produce some temporary benefit.

The Anterior and Posterior Lobes of the Pituitary.

Deficiency of the anterior lobe of the pituitary is believed to produce Fröhlich's syndrome—namely, infantilism associated with obesity and torpidity. Cushing⁷ found that large doses of the dried lobe by the mouth produced benefit in this condition; in one case 1.2 gram daily was required and in another extreme case 20 grams daily were needed. Nothing is known, however, about the chemical properties of the active principle of the anterior lobe.

The posterior lobe contains several active principles of unknown chemical nature, but with very powerful pharmacological actions. The extract is of value in obstetrics as an oxytocic, as a vaso-constrictor in shock, and as a gut stimulant in prevention of tympanites; finally, it produces a temporary curative effect in diabetes insipidus. This last example appears at first sight to be a clear case of substitution therapy, since diabetes insipidus is frequently associated with injury in the pituitary region and with pituitary tumours. Recent work has, however, shown that diabetes insipidus and other symptoms attributed to the destruction of the pituitary by operation, injury, or tumour are probably due to interference with the adjacent portions of the brain.

Pituitary deficiency also produces increased carbohydrate tolerance, and Cushing found that this was abolished by administration of posterior lobe extract. The extract produced its action on hypodermic or oral administration, the relative activities being as one is to four. This is remarkable, for, as regards its other actions, the posterior lobe extract has little or no action if given by the mouth, although it will act if sprayed into the nose.

The above summary shows that only in a few cases is there a satisfactory experimental basis for the practice of substitution therapy. The evidence in the case of dried thyroid and of insulin is practically complete, and the deficiency

diseases for which these extracts are used are comparatively common. Pituitary extracts appear to have a definite effect as substitution remedies, but the condition of pituitary deficiency is rare. The only example of the use of suprarenal extracts as agents in substitution therapy is the temporary beneficial action produced by adrenaline in Addison's disease. Dried parathyroid has an important action in raising the content of calcium in the blood in chronic sepsis, but it is not certain if this is an example of substitution therapy. It cannot be said that there is any definite experimental basis for the therapeutic use of extracts of the gonads.

In addition to the above actions there are various therapeutic uses for endocrine extracts which have nothing to do with substitution therapy. Examples of such actions are the use of adrenaline as a styptic, or as a cardiac stimulant in sudden arrest of the heart, the use of pituitary extract in obstetrics, and the use of dried thyroid to increase metabolism and to decrease obesity.

Nothing has been said of the use of extracts of the spleen, the thymus, and the pineal gland, since in none of these cases does removal of the gland produce any definite syndrome, and hence there is no experimental basis for the use of extracts of these glands as substitution agents.

Extracts of every tissue of the body have been put on the market, and it is possible to obtain from practically any tissue in the body extracts which, when injected, produce pharmacological actions; this does not prove, however, that the glands from which the extracts were prepared have any internal secretion. Splenic extracts, for example, produce increased movements of the gut, and so, indeed, do extracts of many other tissues of the body; this fact does not, of course, prove that the spleen has any influence on the activity of the gut in life, nor is there any reason to suppose that splenic extracts are superior for the treatment of constipation to the numerous other drugs of known composition which can produce a similar action.

A general survey of the results of substitution therapy is undoubtedly disappointing, for the first discovery, the action of dried thyroid, is still of more importance than all subsequent discoveries put together. A comparison of the different endocrine organs suggests that a possible reason for this is that the thyroid gland shows certain unique features which are likely to favour the use of its preparations in substitution therapy. Histological examination shows that the thyroid is constructed to allow of storage of its secretion, whereas the anterior lobe of the pituitary is the only other endocrine gland which possesses a vesicular structure. A possible reason for this peculiarity is that the body is dependent for normal metabolism on a regular supply of thyroid secretion, but the thyroid can only produce thyroxin if supplied with iodine, and iodine is a relatively rare element.

Marine⁶ has shown that a biennial supply of iodide is sufficient to prevent the development of goitre in children living in a goitre district. This suggests that the thyroid stores several months' supply of its active principle. This storage is of advantage in two ways in endocrine therapy—in the first place, very large amounts of active principle can be obtained from the gland, and in the second place a secretion that is stored is more likely to be stable than one which is passed out into the body directly it is produced.

A comparison between dried thyroid and insulin indicates a very great difference in the yield of active principle in the two cases. The human thyroid weighs about 25 grams, and a daily dose of about 0.3 gram of fresh thyroid is sufficient to keep many cretins in normal health (Murray⁷). This is with oral administration, and about a quarter of this dose would probably be sufficient if given hypodermically. These facts indicate that the thyroid stores more than one hundred days' supply of secretion. The human pancreas weighs about 125 grams, and this weight of pancreas will only yield a supply of insulin sufficient for two or three days' treatment of a severe case of diabetes.

The comparison cannot be pressed too far, but it has been tacitly assumed that the results obtained with thyroid medication ought to be repeated with the same ease with every other endocrine gland, whereas the difficulties attending the preparation of insulin, and the comparatively meagre yield

obtained, are probably more nearly typical of endocrine secretions as a whole.

Substitution Therapy in Hyposecretion.

At least three-quarters of any endocrine organ must be destroyed in an animal in order to produce any certain evidence of deficiency disease; consequently it is extremely difficult to obtain experimental evidence of the effects of a partial deficiency of any internal secretion.

Various causes are known which produce destruction of certain of the endocrine organs—for example, tuberculosis of the suprarenals, tumours of the pituitary, lack of iodine in the case of the thyroid, acute infections in the case of the pancreas and parathyroids. There is, however, no evidence for the assumption that partial deficiency in the internal secretions is at all a common cause of disease. Since these glands help to regulate every activity of the body, it is perfectly easy to draw up schemes whereby the symptoms of practically all obscure diseases can be attributed to some disorder of internal secretion, but it is important to remember that such schemes, although interesting speculations, lack any definite proof.

Polyglandular Therapy.

The short review I have given indicates that the therapeutic action of only a few of the endocrine extracts is established with any degree of certainty, and it is interesting to consider what basis of proof exists for the polyglandular therapy that is becoming so popular. Typical polyglandular formulae usually contain some or all of the following preparations: dried thyroid, extract of the posterior lobe of the pituitary, thymus, adrenaline, and extract of testicles or ovaries. The remedy is usually given by the mouth.

Of these constituents the thyroid is beneficent if the patient chances to be suffering from thyroid deficiency, and in other cases there is usually too little present to do any harm. Pituitary extract is inactive when given by the mouth, except as regards its effect in reducing carbohydrate tolerance in cases of pituitary tumour deficiency; this action would be assisted by the thyroid, but it is difficult to see what benefit it would produce for the patient. Pituitary deficiency, as manifested by Fröhlich's syndrome or by diabetes insipidus, is very rare, and outside of these conditions there is no rational indication for the use of pituitary extract other than its usual use as a temporary stimulant to the uterus, gut, or blood vessels. It is not known whether the thymus even has an internal secretion, nor is it known whether its extracts have any therapeutic action. As regards adrenaline, it is not certain whether its secretion is essential for the normal health of the body. In particular we know that the low blood pressure and asthenia in Addison's disease are not simple results of adrenaline deprivation. Adrenaline, when given by the mouth, may be of benefit in gastric haemorrhage or to relax oesophageal spasm, but otherwise there are few actions that it has been shown to exert when given by the mouth. Finally, nothing is known for certain about the action of extracts of the gonads.

I suggest that the administration of a mixture of the above nature is as far removed from rational therapy as is the writing out of a charm on a piece of paper and giving that to the patient to swallow. I have assumed that the extracts on the market have as high a degree of potency as any that it is possible to produce. This is, of course, an unwarranted assumption, for in the case of those extracts where a test of activity has been found, and a correct method of extraction discovered, it frequently happens that some slight error in extraction may result in an inactive preparation being produced; this can occur, for example, with insulin and with extract of the posterior lobe of the pituitary. Obviously in those cases where there is no reliable test for the activity of extracts, it is impossible even to know which is the best method of preparation, and the odds against such preparations having any activity whatever are very heavy.

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