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ORGANOTHERAPY*

BY

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At the outset I must insist that this is a discussion on organotherapy and not on endocrinology in general. I have said before that organotherapy of necessity lags behind endocrinology, which is as it should be; the scientific foundation must be secure before intelligent therapy is possible. Of late, however, therapy has made rapid advances, principally in relation to the sex hormones. This discussion is therefore timely, and should provide a useful antidote to the unscientific exploitation of endocrinology which is rife to-day. Every scientific advance seems doomed to be dogged and shadowed by a new quackery: hypnotism, electricity, light treatment, psychotherapy, and vaccines have each in turn suffered this, and it is too much to expect that biochemistry would escape. I read in a lay paper recently that 90 per cent. of bodily troubles were due to glands, and it was implied that they could be remedied by gland treatment. Organotherapy may well pray to be delivered from such friends!

My remarks will be almost entirely concerned with general principles, for I am to be followed by a number of speakers whose own researches have added to our knowledge and who will speak from their own experience on various topics. It is of interest to me to recall that the whole subject has grown up in my own professional lifetime. For it was in my second year at Cambridge that G. R. Murray first successfully treated a case of myxoedema by thyroid extract. He had been told he might just as well expect to treat tabes with an emulsion of spinal cord, so little had Claude Bernard's conception of internal secretion taken hold of the profession. We must not complain of scepticism, however, considering how much damage credulity has done. But it did seem to me that the late Professor Swale Vincent erred on the side of caution when he maintained that the fact that a juice possessing certain pharmacological properties could be squeezed out of the pituitary body threw no light on the function of the gland. Even as recently as 1921 Sir James Berry announced himself an impenitent sceptic as to the parathyroids having any separate function from the thyroid.

Three Lines of Advance

Starling's conception of a chemical control of the body by hormones which he enunciated in 1905 found powerful support, however, in three subsequent discoveries: first, of vitamins—exogenous hormones, as they have been

called; and, secondly, from the observations of Loewi and of Dale, from which we learned that the secretion of adrenaline and pituitrin by structures of nervous origin are only special instances of a general law—namely, that a chemical substance is liberated at every nerve-ending on stimulation. In Hopkins's illuminating phrase—chemical substances produced locally and temporarily translate for the tissues the messages received through the nerves. The histamine-like substance and the P-substance described by Lewis as playing an important part in manifestations of allergy and of pain constitute another instance of the chemical control of the body. A third line of advance was the discovery by the Needhams and Waddington that Spemann's organizer in the embryo was not cellular but chemical in its activities, and that it was closely related to oestrin. The relation between the stimulants to normal and abnormal growth has been ably demonstrated by J. W. Cook and E. C. Dodds (1934), and we know that from sterols normally occurring in the body a deranged metabolism may produce specific carcinogenetic substances which will stimulate certain cells to wild proliferation. There is indeed considerable overlap between the chemical constitution of certain hormones, vitamins, and carcinogens. Further, the co-operation of organic chemists with the biologists has led to the preparation of synthetic hormones, and it has been found that simpler chemical substances than those existing in Nature may be adequate to produce the biological effect. These basal groups are, in Dodds's happy phrase, skeleton keys which can pick the physiological lock. We are learning, too, that some of them can have other than their normal specific effects—these are, as he says, pass-keys.

Antihormones

Hormones belonging as they do to the innate defences of the body, it was assumed for a good many years that they would not act as antigens. Doubts on the truth of this generalization were first thrown by J. B. Collip's (1934, 1935) observation that parathormone gradually lost its effect on repeated injection. Subsequently the existence of antihormones was established for the gonadotropic growth and ketogenic hormones of the pituitary and suspected for the diabetogenic and adrenotropic hormones. Collip regards a hormone-antihormone linkage as a normal condition, but there is no evidence that these "anti" substances are produced in the endocrine glands (Loeser, 1937). Nevertheless they are not merely precipitin re-

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actions, for they have been obtained against protein-free extracts, and although not always specific for the particular animal, they are absolutely specific for the individual hormone. It is of interest to note that while the antibodies for tropic hormones can be transferred from one animal to another, the antibodies for simpler hormones, such as parathormone, thyroxine, adrenaline, and insulin, cannot be so transferred (Bauer and others, 1936, 1937).

Hormones and Mineral Metabolism

A further advance in organotherapy was made when the interaction between hormones and mineral metabolism was realized. This was first recognized in the instance of calcium and phosphorus in relation to parathormone, but, not long after, the importance of sodium and potassium ions in relation to the adrenal cortical hormone was discovered. It is now claimed by Rivoire (1937) that just as generalized osteitis fibrosa is associated with a parathyroid adenoma, so myasthenia gravis is associated with a thymic adenoma, as indeed others have observed, and that just as sodium does good and potassium harm in adrenal cortical deficiency, so potassium is beneficial and sodium harmful in myasthenia gravis. Dr. R. S. Aitken informs me, however, that he has not found potassium salts of much benefit in myasthenia gravis. When we add to this list the well-recognized association between the thyroid and iodine and also between haemopoietin and iron in metabolism, it is clear that there is a field for research on the connexion between hormones and mineral metabolism. While on this topic it may be relevant to mention H. Zondek's (1935a) conception of hormones circulating in the blood in an inactive form, and only being activated on reaching their destination, where their action as physical catalysts is modified by electrolytes. Thus he claims that calcium inhibits and potassium increases the effect of thyroxine on the cell. Such matters, however, remain chiefly of academic interest at present, but I hope I have cleared the way for a consideration of the general principles of organotherapy.

Three Postulates for Rational Organotherapy

We may lay down these postulates for rational organotherapy:

- A. The gland in question forms an internal secretion.
- B. The active principle or principles of this secretion can be extracted.
- C. A method of administration of this extract is available which will admit of its utilization by the body.

If and when these postulates have been fulfilled, organotherapy may be employed in the following ways.

1. *As Substitution Therapy.*—To replace the absent or deficient secretion of a gland that is involved in a destructive lesion, or where there is relative insufficiency owing to overaction of some antagonistic gland. Here the hormone is intended to produce a chronic effect. It is only necessary to instance thyroid extract and insulin as examples, and I select them for this reason. For success it must be possible for intermittent doses to replace satisfactorily the slow and more constant secretion which normally occurs. Thyroid extract does this most satisfactorily, and the recent work on insulin has been directed towards slowing down its effect by combination with protamine and zinc so as to imitate more closely the conditions obtaining in the body. On the subject of the effective absorption of hormones and the methods of prolonging their action I may refer you to the paper by Dr. A. S. Parkes (1938). It is important to observe that sub-

stitution therapy does not imply that thereby the body may be induced to form its own hormone; indeed, the evidence is all against any such effect.

2. *As Pharmacological Agents.*—Where their known physiological action may be useful, quite apart from any recognizable defect in the patient's own glands. Here a sudden effect is usually aimed at. The injection of adrenaline for the relief of an asthmatic paroxysm is a well-recognized example of this. The production of insulin shock in the treatment of schizophrenia might be cited as another example, though recent observations (Salm, 1937) on the damage which can be wrought on the nerve cells by this procedure should give us pause.

3. *As an Antagonist to Another Hormone.*—Here we can instance insulin in the treatment of hyperthyroidism, pitressin and adrenaline as antagonists to insulin, also oestrin in the attempt to neutralize an overacting pituitary, which has perhaps been more successful in menopausal disturbances than in other directions, though Kirklin and Wilder (1936) claim success for oestrone in the relief of acromegaly. Zuckerman showed that testosterone suppressed ovulation in monkeys, while Loeser found clinically that it led to atrophy of the endometrium and was of therapeutic value in menorrhagia. Levy Simpson (1938) has also used it with some success as a method of neutralizing the thyrotropic hormone in hyperthyroidism.

4. *To Influence General Metabolism.*—Thyroid may certainly help to quicken up general metabolism if it is desired to do so, even in the absence of hypothyroidism. Insulin, adequately covered by dextrose, is often helpful in anorexia nervosa and other wasting diseases. It is claimed for oestrin that it has a favourable influence on impaired carbohydrate metabolism; indeed, Glen and Eaton (1938) found that dihydroxyoestrin increased sugar tolerance in a severe insulin-resistant case of diabetes. But as this effect is presumably antagonistic to the diabetogenic pituitary hormone it should perhaps be classed under heading No. 3.

5. *As an Attempt to Utilize Antihormonal Activity.*—There are two possible therapeutic applications of anti-hormones to correct over-activity of endocrine glands: (a) *passive neutralization* by means of the antihormone produced in another animal by injecting it with the corresponding hormone, and (b) *active antagonism* by injecting the patient with sub-threshold doses of the hormone in question and thus causing him to produce his own antihormone. The first method has had some limited success experimentally, and Loeser (1937) found the antithyrotropic hormone effective even when given by the mouth. I am unaware, however, of any clinical successes by this method. The second method, although imitating vaccine therapy, does run the risk of aggravating the disease. Hertz and Hisaw (1934) have succeeded with sub-threshold doses of gonadotropic hormone in rendering an animal's ovaries resistant to subsequent large and usually effective doses.

It must be admitted, however, that antihormonal action has so far proved a hindrance rather than a help to organotherapy, particularly so far as the pituitary tropic hormones are concerned. Thus Spence and Witts (1938) found that patients soon became resistant to the thyrotropic hormone, and were able to demonstrate the presence of the antithyrotropic hormone in their serum. It seems generally advisable also to give the growth hormone periodically with intervals of rest, in order to avoid the development of the antihormone.

6. *Employed Empirically.*—As time goes on we may expect to find instances originally placed in this category

transferred to others. Indeed, this process is actually in progress. Thus while I can offer no rational basis for the relief given by pitressin for the pain of herpes zoster and its frequent neuralgic sequel (W. H. Marshall, in a private communication), the influence of parathormone on intestinal colic may perhaps be explained by the sedative effect of hypercalcaemia on muscular tone. The rationale of the treatment of chronic mastitis by oestrin with or without the addition of prolactin is not yet obvious, since both these hormones increase the activity of the breasts. The relation between oestrin and the condition of the nasal mucosa is, however, of special interest. In animals the olfactory sense is clearly associated with sex, and the observations of Mortimer, Wright, and Collip (1937) on the effect of oestrin in the treatment of atrophic rhinitis are important. This has led A. S. Hoseason (*Journal*, October 1, p. 703) to call attention to the opposite condition of vasomotor rhinitis, and compare it with the condition produced experimentally in monkeys by overdosage with oestrin.

I do not, however, intend to say much about organotherapy by sex hormones, because, this being at the moment the most rapidly advancing branch of endocrinology, some of the subsequent speakers will devote the whole of their contributions to it. I would, nevertheless, point out that the increasing use of oestrogenic substances in the treatment of disorders in the male supports Dodds's conception of the "skeleton key" action of certain hormones.

Deleterious Effects

That self-medication by thyroid extract often leads to disastrous effects is generally recognized. Any really active therapeutic agent is capable of misuse. The danger of repeatedly inducing insulin hypoglycaemia has already been referred to. Parathormone can clearly have a destructive effect upon bone and may induce the formation of renal calculi; fortunately these effects are partially limited by its exciting the production of an antihormone. The administration of oestrin for the vulvovaginitis of children has been followed by precocious puberty, both physically and psychically. Dodds and Noble (1937) have demonstrated the harmful effect of repeated injections of pituitrin on the gastric mucosa. Whether continued injections of adrenaline can produce arteriosclerosis has been much disputed. On the whole it seems unlikely. I saw one striking case under the care of Dr. George Graham where a young woman developed a systolic blood pressure of 280 mm. Hg after frequent injections extending over two years, but in view of the rarity of such a sequence she may have had a coincident malignant hypertension. I think the experimental evidence as to the carcinogenetic effect of oestrin need not lead us to fear a clinical counterpart; it has been calculated that it would take fifty years for its ordinary administration to have this effect in human beings.

Routes of Administration

(a) *Oral*.—The early triumphs of thyroid medication by this route led to disappointment when it was found that it was not equally effective for other hormones. There seems to be a good case for the efficacy of this method for certain sex hormones, though about five times as large a dose is required compared with injection. Haemopoietin and ventriculin may fairly be regarded as hormones, and are undoubtedly effective given thus. As to certain properties of anterior pituitary, I must confess that *pace* the pharmacologists I have seen effects follow

its oral administration too frequently to believe they were merely due to coincidence. But here I expect I am in a minority.

(b) *Nasal*.—As the post-pituitary is an upgrowth from the nasal mucosa, it was suggested by Blumgart that this route might be effective for pituitrin, and so it proved to be. It remains true, however, that the

(c) *Subcutaneous* is the only effective route for the majority of hormones, reinforced by

(d) *Intravenous* administration in emergencies such as diabetic coma.

(e) *Rectal* administration is seldom called for, and though advocated for insulin it offers quite as great drawbacks as the hypodermic syringe.

(f) *Cutaneous*.—B. Zondek (1938) has called attention to the fact that the oestrogenic hormone dissolved in benzol, ether, or alcohol is completely absorbed by the skin.

Receptivity of Hormones by the Tissues

Although intensive study has been made of the pharmacology of hormones, there is evidently another aspect which has so far been little investigated. That is the receptivity of the tissues. How this normally varies in accordance with the needs of the body can be succinctly illustrated by the metamorphosing tadpole. Under the influence of thyroxine the cells of the gill-covers atrophy, while at the same time the limb-buds grow actively. This may perhaps be regarded simply as an example of thyroxine speeding up metabolism in the direction in which it is normally going, but other instances cannot be so simply explained.

Some thirty years ago Langley and Elliott independently postulated the existence of a receptive substance between the nerve-ending and the tissue as necessary to explain the facts then known. If such a postulate was required then, how much more is it needed to-day! Just as the appropriate chemical material, such as pilocarpine or atropine, may get into this receptive substance, so may a toxin. G. N. Myers has shown that a therapeutic drug may seize on the receptive substance and thus bar the way to the ingress of the toxin. It seems to me that the pharmacology of the future will have to concern itself with the natural history of these receptive substances, and find out in what manner they can be helped by drugs, both positively, by facilitating their reactions, and negatively, by blocking the way against the entrance of toxins. Nor is this topic remote from my subject, for H. Zondek (1935b) maintains that the absorption of a hormone, such as thyroxine, is decreased in the presence of narcotics, such as the barbiturates, which are able to adhere to the cell surface and thus to displace the hormone from it. But it is also germane to my subject in a wider sense. We are still entirely without any conception why a particular cell should be sensitive to a particular chemical substance or why the same substance should augment the activity of one type of cell and inhibit that of another. The nature of these receptive substances is a problem to which many minds are beginning to devote themselves. The importance of the responsive capacity of the receptor tissues was clearly indicated by Harrison in his Harveian Lectures for 1934. He showed that when transplantation is effected between embryos of species of different sizes the transplant responds according to its inherited growth capacity rather than to its new endocrine environment. As Keith pointed out some years ago, the partial gigantisms in certain cases of hyperpituitarism can only be explained

on the theory that the locally hypertrophied tissues had developed a special sensitiveness to the growth hormone. H. M. Evans has shown that the response of the dachshund and of the sheep-dog to injections of the pituitary growth hormone is entirely different. Indeed, if such things were not so, it would be difficult to account for structural plasticity in the hands of the breeder.

It must have fallen to the lot of everyone who has treated cases of pituitary obesity to find some patients entirely refractory to treatment identical with that which has been successful with others. Yet clinically no difference could be detected between the two groups. I know that there are authorities who maintain that obesity can always be reduced by diet alone; I do not know if they would add that the patient can also be kept in good health. I believe that retention of water is one factor in preventing reduction of weight, and I sometimes speculate on the possibility of putting on weight by assimilation of oxygen: how otherwise does the hibernating animal become heavier? But apart from such controversial matters, it seems clear that cases of obesity of admittedly endocrine origin respond so differently that some difference of receptivity is probable.

In concluding this necessarily summary introduction to the discussion may I express the hope that research on the synthetic hormones may effect two things: first, the discovery of simple basal groups which can produce the biological effect and yet escape disintegration by the digestive juices; and, secondly, reduce materially the cost of production. At present the cost of many is prohibitive except for the very rich and for the hospital class.

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L. Rizzi (*Riforma med.*, 1938, **54**, 1222), who records an illustrative case, states that in most of the cases of pituitary haemorrhages on record there are minute punctate haemorrhages indicating toxic degeneration, or merely sudden increase of pressure, corresponding to the small haemorrhages observed in all the other organs. Large pituitary haemorrhages are very rare, and their origin is obscure. Almost all cases of this kind have shown old haemorrhages, which had given rise to more or less definite pituitary syndromes. The present case was that of a woman, aged 49, the subject of diffuse glomerular nephritis with hypertension, who six days before death developed severe cerebral symptoms due to uraemia. In addition to well-marked arteriosclerosis and renal sclerosis the necropsy showed a large haemorrhagic cyst in the hypophysis. The cause of death in this case was the compression of the mid-brain or the general endocranial hypertension produced by the haemorrhage.

TREATMENT OF TUBERCULOSIS IN GUINEA-PIGS WITH SULPHANILAMIDE

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The experiments described in this paper were carried out in an attempt to repeat the work of Rich and Follis (1938), who obtained considerable inhibition of the development of tuberculous lesions in guinea-pigs infected with a human strain.

Technique

Infection of Guinea-pigs.—Suspensions of actively growing (six-day) cultures from Petraghani's medium were injected subcutaneously into the right leg of guinea-pigs which averaged 400 grammes in weight. Two virulent strains were used, as follows:

Human strain, R. 2: Twenty guinea-pigs received 0.05 mg. of culture and twenty 0.5 mg.

Bovine strain, BV. 28: Twenty guinea-pigs received 0.01 mg. and twenty 0.1 mg.

With the aid of an opacity standard tube we estimated that 1 mg. of culture contained approximately 2,000 million tubercle bacilli.

Treatment with Sulphanilamide.—Half the animals in each group were kept as controls and half were given sulphanilamide (50 per cent. suspension in 5 per cent. gum arabic) four times daily by mouth. A total of 500 mg. (100 mg. at 9 a.m., 1.30 p.m., and 5 p.m., and 200 mg. at 10 p.m.) was given daily for five days; these doses were halved from the sixth to the forty-second day, when all survivors in both treated and control groups were killed. Unlike Rich and Follis, who deposited the drug in the cheek pouch, we induced the swallowing reflex by ejecting the suspension from a syringe on to the back of the tongue and pharynx. Almost all the material thus administered was retained.

Toxic Effects of Sulphanilamide

The treatment we employed for the first five days of the experiment—namely, 500 mg. daily—was regarded as the optimum therapeutic dosage by Rich and Follis, who noted evidence of overdosage, however, in certain guinea-pigs which had been treated for three to six weeks. We reduced the dosage to 250 mg. after the fifth day, because some guinea-pigs undergoing treatment soon became ill with characteristic toxic signs—loss of weight and temporary paralysis.

The average weights of the treated and control groups of guinea-pigs were approximately the same (400 grammes) at the beginning of the experiment, but the treated animals lost an average of 50 grammes during the first week of treatment, whereas the weights of the untreated controls remained stationary. When dosage was reduced towards the end of the first week the general condition of the treated animals improved, although they remained lighter than the untreated controls. Unfortunately, in this preliminary experiment we did not continue to weigh the animals at weekly intervals.