ENDOCRINE GLAND EXTRACTS.

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ENDOCRINE GLAND EXTRACTS.
Their Manufacture and Use.

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Although throughout the literature on the endocrine glands and their application therapeutically there is found much wisdom, both empirical and based on experiment, the busy medical practitioner can find little of a purely practical nature. There is little to be found concerning the quality of these products, nor is there much to be found regarding the mode of their administration. Of the former, I shall briefly point out some of the essential features concerned in the collection, the separation, the purification, the standardization and marketing methods of these substances, pointing out, as I go along, those features which seem objectionable to me as a clinician, in so far as they are likely to render the results somewhat confused. Of the latter, whatever I say is based on my own personal experience with sick human beings. I do not assert for it any sort of finality nor superiority over other methods, but it is one way of using these products, and I feel sure that in the criticism of this method, far better ways of therapeutic procedure will be developed.

None of the commercial endocrine products are obtained from the human species, for obvious reasons. So all through our therapeutic work we must bear in mind that, whatever product we are using, it is a foreign proteid when introduced into the human body, whether the introduction is by mouth or hypodermically. To the slaughter houses
we must go for our raw material, and in the United States there are one hundred and forty-seven independent packing houses, all of which own one or more slaughter yards, but in spite of this seemingly great supply ground it appears that the demand for pituitary glands, for example, has increased to such an extent in the last few years that at the present time one of the largest pharmaceutical houses is already arranging to take over the supply of these glands from foreign markets, especially those in the Argentine Republic. As a rule the raw materials are gathered from animals which are perfectly healthy; these animals pass the United States Government inspection as well as the inspection by the slaughter houses' own officials before they are killed. The raw glands are removed by hand from the carcass and immediately packed in ice and delivered to the laboratories where they are to be refined and prepared for therapeutic administration. It is a fact that these raw glands deteriorate much more rapidly at any temperature above the freezing point than do the ordinary animal products. So marked is this characteristic that one of the greatest packing houses in the country refuses to send any of the crude glands away from its own establishment, because it has learned that in a refrigerator car, traveling but a short distance, a lot of these glands may become unfit for use, although the conditions were such that the balance of the material in the car, ordinary meat products, were unaffected. In this particular house the crude glands are carried immediately upon separation from the carcass to the laboratory, and only twenty-four hours elapse between the slaughter of the animal and the complete desiccation of the gland. Naturally, this happy state of affairs is not universally true. Some pharmaceutical houses, on account of their geographical position, are compelled to obtain their crude glands from considerable and varying distances, trusting to the preservation by refrigeration in their shipment.

One manufacturer who attempts to market his products upon order only, told me that he keeps the crude glands in a frozen condition until they are required. The question arises in my mind as to whether or not big differences in the finished product are not in some cases due to the differences in the speed of transportation and the refrigeration. After these glands are received by the various laboratories they are dissected out by hand, freed from as much adventitious material as possible, and then ground or macerated by hand or by machine, following which the material is dried. It is in this process of drying that many variations appear. One manufacturer dries with warmed air at normal barometric pressure. One manufacturer dries in vacuum with a temperature of 140° F. Another in vacuum with a temperature between 50° F and 60° F. Another with a temperature of 90° F., and another with a temperature between 40° F. and 50° F. Naturally the time required for drying varies in proportion to the height of the temperature and to the rarity of the atmosphere in which the product is dried. It would seem that in all probability certain qualitative changes must appear in the finished product which can be ascribed to these variations in the drying temperatures. It would seem that in this process as low a temperature as possible should be maintained, and that the drying made as speedily as possible by the use of vacuum dryers.

The next step in the manufacture is the process of defatting. Here, again, methods of wide variation are employed. In one laboratory I am told there is little or no defatting except when the material looks or feels particularly greasy to the individual who is responsible. In another laboratory there is no defatting practised for any of their products. Still another firm subjects all their material to a petroleum ether process, while still another uses for this process either gasoline or acetone or carbon tetrachloride. While it is a fact
that the active principle of the posterior lobe of the pituitary gland is insoluble in ether, petroleum ether, chloroform and absolute alcohol, we have no data available for basing a similar statement regarding those glands for which we have no tests of standardization, and in all probability certain quantitative and qualitative changes do take place in this variety of processes which have a decided influence on the finished product. The removal of fat, particularly when excessive, is certainly desirable, inasmuch as its presence would lead to the development of rancidity and offensive odors which might prove disastrous in the administration. Altogether it seems that the medical profession would benefit by being informed exactly which agent was used in this process for each particular finished product. In this way, clinical results would become more accurately obtainable.

Following this defatting process the material is, as a rule, further pulverized and prepared for the market, being mixed with milk sugar and finished either in tablet form or in capsules. Two factors enter into the manufacture of tablets which might have an effect on the quality of the finished product, the first being the necessity of using a liquid so as to give the mass a certain cohesiveness (alcohol is at times the fluid used, and it conceivably might alter the nature of the enzyme); the second is the theoretical possibility that the pressure necessary for the stability of the tablet might have an influence qualitatively.

The question of gland quantity incorporated in the various tablets is answered in a number of ways by the different manufacturers. As a rule these tablets represent a certain amount of the fresh gland. On the other hand, certain commercial products represent the indicated amount of the dried gland, and, finally, one manufacturer computes his doses in such a manner that one tablet bears the same ratio by weight to the entire gland as the weight of the average human being bears to the weight of the animal from which the tablet material was taken. In other words, taking a tablet of entire pituitary gland extract for example, the extract in one tablet equals by weight one tenth of the entire pituitary gland of the steer; based on the fact that the average human being of 150 pounds equals one tenth of the weight of the average steer, 1,500 pounds.

In this connection it is interesting to note that approximately five pounds of fresh pituitary glands are obtainable from one thousand head of cattle, which quantity, when desiccated, is reduced to one pound in weight. In the case of pineal glands, two thousand heads of cattle are required to supply five pounds of the fresh or one pound of the dry gland. Fifty sheep supply one pound of fresh thyroid gland, which is reduced to three drams on drying. Whether it is preferable to supply these endocrine extracts in tablet form or in capsule form is a question, but it would seem probable that the material in the ordinary uncoated tablet is liable to a greater amount of deterioration, due to the processes involved in tablet manufacture as well as to oxygenation, than when the fresh powder is protected in a capsule. Another danger which the tablet carries is that it places a peculiar restraint upon the physician's therapeutic endeavor. The minimum quantity he will use is fixed by the manufacturer and in many instances the maximum by the doctor's own bad twice daily and thrice daily habits. I shall refer to this again.

Personally, I think the practitioner should prescribe the powder, which is supplied in bulk, in capsule form in such quantities and in such combinations as he believes fit each individual case. The danger of using doses calculated on a weight ratio lies in the fact that individual animal glands show considerable active principle variation in those cases where such determinations are possible.

Turning our attention more particularly to the
specific glands, we find that the only three preparations which are standardized are the posterior lobe of the pituitary, the thyroid, and the extract of the medulla of the adrenal glands, known as adrenalin. This last, by the way, being a natural, not a synthetic product, as many believe.

The extract of the posterior lobe of the pituitary is removed from the dried gland tissues in aqueous solution, standardized and placed in ampoules. Some of these preparations contain a preservative, while others do not. Here, as in all other ampoule preparations, great care must be taken to use only a neutral glass, which is at the present time obtainable. This pituitary solution is standardized according to the requirements of the U. S. P. so that "one mil of solution of hypophysis diluted 20,000 times has the same activity on the isolated uterus of the virgin guineapig as 1:20,000,000 solution of betaiminazyl-ethylamine hydrochloride (histamine) when tested as directed by the United States Hygienic Laboratory" according to the method of G. B. Roth. This observer (1) finds that in spite of this standardization a great variation exists among the commercial products. This method is objected to on account of its difficulty, because histamine is not absolutely stable, and, finally, because the exceedingly high dilutions necessary for the execution of this standardization render the method susceptible to proportionately great error. An alternate method of standardization is offered by R. A. Spaeth (2), who proposes that the standard used be a Locke solution plus the addition of an excess of potassium chloride. It is apparently a better method. It must also be remembered that various lots of this extract differ not only in their oxytocic principle, but also in their blood raising principle. The two do not run parallel; some are rich in one and poor in the other, whereas the reverse may be true, so that in the preparation for the market of this extract the careful manufacturer must adjust his various lots so as to bring the final product up to this dual standard. And the full sphere of pituitary gland extracts does not depend solely upon these two principles.

In the marketing of this particular product we find a great variety of strengths. Ampoules containing one half, one, two, three, four or six times the U. S. P. strength are purchasable; some are called surgical and some obstetrical, although they contain exactly the same material. One firm markets the same strength solution but in small and large sizes. This scheme, although making for simplicity, is objected to on the ground that in some instances excessively large amounts of the extract would have to be used to accomplish the desired effect. Some contain a chemical preservative; others do not. At the present time the U. S. Hygienic Laboratory does not supply the manufacturers with a standard sample. In the preparation of all pituitary gland extracts, that of the steer is the only gland used. As you know, the steer is the castrated adult male. The castration causes many structural and functional changes in the animal, for the most part due to alteration of the pituitary gland secretion. Although this fact has probably no bearing on the obstetrical or surgical uses where introduction of this gland is made purely for medico-physiological effects. It would be interesting to know if the glands of the female and the uncastrated male would give different results in certain medical situations than do the extracts obtainable.

In the manufacture of thyroid gland preparations, the gland of the sheep alone is used in one instance, in another that of swine, but in all cases the standardization is done according to the iodine content. The U. S. P. IX states: "The thyroid glands of animals which are used for food by man, freed from connective issue and fat, dried and powdered, and containing not less than seventeen hundredths per cent. nor more than twenty-three hundredths per cent. of iodine in thyroid combination." In a
very interesting paper recently published, Tatum (3) brings out the fact that the "ratio of the per­
centum of iodine in the cells to the iodine in the
whole gland appears relatively constant for pigs,
sheep and beef thyroid content." His figures also
show that the pig thyroid contains the greatest
amount of iodine, that the beef thyroid the least,
while that of the sheep falls in between the two,
and further that some individual animals possess
iodine in their thyroid glands four times as much
as others do. Probably the iodine content will not
be the final criterion upon which is based the deter­
mination of the efficiency of the thyroid prepara­
tions, and at present one laboratory is devoting much
time to other standardization methods. In a paper,
Fenger (4) finds that in the thyroid of the fetus
iodine is present in greater concentration than in
the adult gland. The same is found true regarding
the active principle of the adrenal gland. Surely
the active life of the adult throws a greater stress
upon these glands than does the sheltered life in
utero, and for this reason they must be more active,
and in different ways, yet according to our present
standards they would seem to be less so. Janney
and Henderson (5), in a recent article, state that
"Treatment of hypothyroidism is best carried out
with Kendall’s thyroxin and controlled by estima­
tion of the basal metabolic rate."

The source of the other gland material varies
with different manufacturers, some use the thymus
gland of the sheep, others that of suckling calves.
Orchitic substance is derived from rams in some
instances, in others from bulls. In the case of
ovarian extract, some manufacturers use the ovary
of the cow, others the sow, while in the case of
adrenal gland extracts no difference is made between
the sexes, male and female glands alike being used.
It seems that these variations could at least be
indicated by the manufacturer, and I feel that this
is necessary, because these differences must exert a

Strass: Manufacture of Endocrine Extracts.

profound physiological effect in their administra­
tion. In the case of the corpus luteum the ovary
of the pregnant cow is generally used, although some
firms use both that of the pregnant cow and the sow,
while others the sow alone. The latter animals are
extremely difficult to obtain, inasmuch as the packers
are very loath to kill them, in view of the fact that
within a few weeks the resulting litter of pigs will
be of greater value than the ovary alone would be.
On the other hand, in herds of cattle it is found
that over sixty per cent. of the cows slaughtered
are pregnant. Naturally the only corpus luteum
which should be used is that obtained from pregnant
ovaries; and a careful differentiation should be made
in the marketing of the products labeled whole
ovary and ovarian residue.

The question of the form in which these products
should be prescribed must be decided by the physi­
cian himself. His choice lies between the powder
in capsule form or the compressed tablet, either
coated or uncoated, and in some few instances in
ampule solution by the hypodermic method. To
my mind the method of choice is the former, as may
be concluded from certain facts outlined above. In
all probability a different effect, clinically, would be
obtained when these extracts are used hypodermati­
cally. Opinion today, however, is fairly well agreed
that perfectly satisfactory results are obtainable
when these products are given by mouth. Their
administration is naturally required in some instances
over long periods of time which would render the
hypodermic method unsatisfactory.

The next question which the practitioner must
decide is whether he will use single gland extracts
alone or in combination with other gland extracts,
or botanical and mineral medicinal substances put
up in capsule form to meet the requirements of each
particular case and situation, or whether he will
resort to the easier way of prescribing certain stock
shotgun mixtures as they are marketed by certain
manufacturers. In support of the latter method the theory is advanced that the body cells have the “capacity to pick out the hormones that are needed and in the amount that they are needed” (6). Frankly, I consider this a misconception, for if it were true it would, for example, be evidently impossible to give anyone an overdose of thyroid extract, which unfortunately is not only true but all too frequent. Of course, it is nearer the truth in the case of normal healthy individuals, but the physician is not called on to prescribe for them.

The effect of endocrine extract therapy is threefold: Homostimulative, heterostimulative, and substitutive. When you introduce thyroid gland extract into the human body you stimulate that individual’s own thyroid gland to a changed activity, and, further, you stimulate those other endocrine glands which are especially associated with his thyroid mechanism. On the other hand, when a cure of cretinoid states has been accomplished by thyroid extract feedings, the therapy has been substitutive. This is my belief, and it is the tripod upon which I base all my efforts of endocrine extract therapeutics.

Further, it is probable that most of the benefits obtained with endocrine extract administration are the result of qualitative changes in the individual’s own endocrine organization, and in those cases where the results are due to quantitative endocrine introduction, it is fair to assume that the individual’s own gland is the seat of considerable organic change.

Presuming that this is true, that most of the changes brought about are purely qualitative, it is fair to conclude that there is little need of large quantitative dosing. As is known, there is a tendency of late throughout all therapeutic work toward smaller and smaller doses, and it has been my experience in the therapeutics of endocrine extracts to obtain brilliant results after a single minimal dose. Interestingly, that same individual may show no reaction to a subsequent similar dose. E. A. Schäfer (7) states that “Others have obtained different results, and state, although in dogs small doses of extract from an exophthalmic goitre may cause increased rate of heart beat and some rise of blood pressure, this is soon followed by the opposite condition. They therefore hold that the symptoms are produced, not by excess of normal thyroid secretion circulating in the blood, but as the result of the production of a perverted secretion (dysthyroidism).”

Every individual is an individual unto himself alone, endocrinologically. It seems to me to be a sad commentary upon the fairmindedness of physicians when they insist that only those methods which have the seal of official approval may be ethically included in their armamentarium, so let us not limit ourselves to one grain or two grains and so on, as the case may be, but in the first place attempt to obtain a purely qualitative reaction.

We know from chemistry that many chemical reactions are much influenced by the presence of substances which do not themselves seem to take a part in the reaction and are left apparently unchanged after it has ceased. This is known as the phenomenon of catalysis. These catalytic agents may either increase or retard chemical action. In all probability some of the physiological expressions of endocrine activity are due to the possible catalytic nature of these ferments, inasmuch as this catalytic attribute does not depend on quantitative factors let us prescribe accordingly. Begin with a dose approximating one millionth of a grain, a dose so small as this, strange as it may seem, should not be given more frequent than every few days. If after a trial or two no reaction is noted, use a thousandth of a grain in the same way; from a thousandth of a grain ascend quantitatively to a hundredth of a grain, a tenth of a grain, a half a
Grain, and one grain, and up. The greater the quantity the more frequent may be the administration. I always begin with infinitesimal doses because, from my experience, such doses have no effect when their administration follows that of the large material doses, in all probability because of the presence of antibodies in the blood stream. Possibly, if endocrine extracts from the human species could be obtained, such antibodies would not be formed, so we must always remember that, no matter how careful the preparation has been, we are introducing into the system a foreign protein. Infinitesimal doses probably act through homostimulation of the similar human gland, whereas a large material dose, while it may act in a similar way, must also cause a decided disturbance of the remaining glands of the individual's endocrine chain by suddenly throwing into the blood stream such an unusual amount of a particular gland enzyme. Between doses wait until the patient's reaction is completed. It is poor practice to increase dose quantity and frequency because good results are obtained from small doses. Small doses act differently than do the large.

There are reasons to believe that in any therapeutic procedure the infinitesimal dose and the material dose have reverse effects, to wit: opium, which in material doses causes constipation, while in infinitesimal doses often causes intestinal evacuation, and while this latter reaction may be brought about only through the relaxation of an intestinal spasm, the fact, however, remains that you have obtained reverse effects by a quantitative variation of the dose alone, no matter how logical the explanation may seem. The entire school of homeopathy is founded on a presumption of this kind; another similar example is the therapeutic use of tuberculin in the treatment of tuberculosis. Finally, in the light of our ever increasing knowledge of the various anaphylactic phenomena, we no longer can deny the fact that massive changes may be caused by the introduction of minute quantities of certain foreign proteids. In this connection we again find in the last mentioned volume on pages 68-69, "Trendelenburg estimated the amount of adrenalin in the blood of the suprarenal vein of a cat, and found that on the average .003 mg. was passed out of the two organs each minute. From the data thus obtained he reckons that about five mg. to the kilo body weight is formed in twenty-four hours. After draining off a large quantity of blood and thus causing a considerable fall of blood pressure, the amount of adrenalin passed a minute was not increased. G. N. Stewart states that massage of the suprarenals leads to the passage of an increased quantity of adrenalin into the blood. When the massage is light a depressor effect is cause, when vigorous a pressure effect, but, according to Hoskins and McClure, there is never so large a pressor effect as with ordinary therapeutic dosage. Hoskins and Rowley find that administration of adrenalin does not increase the excitability of the vasomotor nerves to faradization, but rather tends to depress it. With regard to the amount of adrenalin required to produce a physiological effect upon plain muscle, it may be mentioned that Cannon obtained inhibition of a strip of intestinal muscle with a solution containing one in twenty millions, and Janeway and Park observed inhibition of a strip of coronary artery of the sheep with a solution of one in fifty millions."

In treating your patient it is always essential to attempt to determine which gland is essentially to blame from the clinical picture presented by the patient, and that particular gland is used as the therapeutic basis. It should, however, be remembered that these disturbances cannot ever possibly be monoglandular and a determination must be made by the clinician of the other weak spots in the endocrine chain. In this connection a résumé of the patient's symptoms must be made at every visit because even though, for example, an indication for
ovarian help may be present at the first examination of an individual who is essentially disthyroidal, such ovarian disbalance may be partly or entirely overcome by the administration of the original thyroiadal medication.

For routine use, small doses of thyroidal extract, even though the diagnosis seems to place the chief blame in another direction, may prove of great value in uncovering certain unsuspected clinical manifestations, because it is probable that the thyroid gland occupies a hub position in the endocrine chain, may help reveal the weak spots more clearly. At the present time this initial thyroid feeling is used in the attempt to discover cases which are known as slightly hyperthyroidal. Of course this may be of some value, but personally I believe that in those cases which are actually hyperthyroidal the introduction into his system of such an initial dose does him an actual great harm, and further even though a positive result is obtained, there are some cases which, although they give a positive reaction to such a test, are not basically hyperthyroidal at all, as the tests would make the observer believe, but the overactivity of the thyroid gland is either relative or compensatory. In both of these groups a successful therapeutic result can only be obtained by correction of the outlying glands which in their disorder have caused only an apparent overactivity of the thyroid gland.

After the clinician determines which gland is essentially to blame, and if the difficulty seems to be a purely functional one, correction should be begun with infinitesimal doses, at intervals, as before described. These doses are to be increased quantitatively, and parallel with the quantitative increase should be an increase in the dose frequency. In this connection it is interesting to recall that the equivalent of one millionth of a grain is to be found in the 1X potency. It must always be remembered that when the desired result is obtained, therapy must cease immediately and entirely. This I have pointed out in an earlier article (8).

Finally, although it is being more and more freely admitted that an individual's endocrine tonus determines to a very large extent both his psychic and physical life, one must be ever cautious in the therapeutic application of this knowledge and always remember that this entire field is still in the very early stages of its development.

SUMMARY.

Two points I wish to emphasize again:

1. Let the manufacturers announce the exact nature of their products in all its detail so that therapeutic results may be better understood and thereby stabilized.

2. Let the physician be more willing to relinquish his very old and routine administration habits and adopt a more open mind in the use of these delicate endocrine extracts.

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