

CHAPTER XII.  
THE INTERNAL SECRETIONS AND  
ORGANOTHERAPY.

THE FUNDAMENTAL PRINCIPLE OF THE ACTION OF  
ORGANIC PREPARATIONS.

AMERICAN textbooks afford no clue as to the manner in which the thyroid gland carries on its functions. Some writers hold that the thyroid and parathyroids, by means of an internal secretion, "exercise an important control over the processes of nutrition of the body"; others contend that the purpose of these organs "is to neutralize or destroy toxic substances formed in the metabolism of the rest of the body." Others again assert that it increases metabolic activity, especially catabolism. I have submitted ample evidence to the effect that the thyroid influences all these functions; but *how* does it do so? This is the feature that I have supplied in the present work. If the reader will take into account the fact that the above divers functions, attributed by different groups of investigators to the thyroid, are *all* explained by the one rôle I have attributed to this organ—that of sensitizing the organic phosphorus of all tissues—he will surely concede that my position must be a strong one. And this may be said to apply to the other organs analyzed in this work. The analyses I have submitted have not been destructive; they have proven constructive; they have shown that different sets of experiments and clinical observations which apparently divided several groups of investigators upon each question into as many antagonistic camps were all, when interpreted from my viewpoint, conciliated and harmonized into a consistent whole.

In their application to organotherapy, my views are submitted to a still greater test: they are shown to explain *all* the therapeutic effects of preparations of the organs studied in the present work, namely, the thyroid, parathyroids, adrenals, pituitary, pancreas, spleen, and thymus. Certain organs, such as the kidneys, ovaries, and testicles, whose internal secretions have

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been specifically studied, may now be included in the list, for there is good ground for the proposition, at least, that their organic products should not be regarded as special secretions, but as the product of a single kind of secretory cells that are common to many organs, the adrenal cells.

If our object to place pharmacology on a scientific footing is ever to be realized, we should insist, whenever an agent is to be tried therapeutically, upon a preliminary determination of its identity as a chemical body. Thus only will it be possible for us to establish its physiological action on a solid basis. In drug therapy, this important feature has been carried out to a considerable extent, and what we know of the physiological action of most agents derived from plant life has been acquired since their active principles have been isolated and made the basis of experimental and clinical study. Just as opium contains various principles—morphine, apomorphine, codeine, etc.—so do animal extracts contain a multiplicity of substances, cellular and plasmatic, and also products of cellular metabolism capable of provoking physiological effects; but here very little effort has been made to isolate the truly useful principles. Hence the confusion and empiricism which has always surrounded the use of these agents.

All this applies to organotherapy as it does to pharmacal agents. It is unquestionably true that we have among the twenty and odd animal extracts that have been proposed a few, at least, which are capable of affording relief where no other class of agent will act—thyroid preparations in myxœdema and cretinism, and adrenal extractives in Addison's disease and hæmorrhage, for example. The adoption of a systematic line of study in the direction proposed seems to me to facilitate the discovery of additional useful applications of these agents, or, at least, to give their use in practice a more rational basis.

Important in this connection is the identification of the true organotherapeutic preparations. By the "true" agents I mean those which can be used intelligently, that is, with knowledge of the physiological effects produced, because their active principles are known. Thyroid extract belongs to this class, since we know that its action is due to the iodine in organic combination its secretion contains; adrenal preparations like-

wise are included because their active principles, whether epinephrin, suprarenalin or adrenalin, are also known. Conversely, we have a large number of organic preparations that are used blindly, without knowledge of their components, which may number from five to twenty or more, in almost any disease related directly or remotely with the organ from which the extract is obtained. Mammary extract can be cited as an example of these agents. They are hardly entitled to a rank much above that of empirical nostrums until rendered fit, by their sponsors, through chemical, pharmacological, and clinical researches, to be taken up by the profession as legitimate pharmaceutical agents.

That so desirable a task is not impossible of accomplishment may readily be shown. We shall take as examples those which, besides the thyroid, parathyroid, and adrenal products, whose active agents are familiar to every one, the four which have stood out most prominently in the history of opotherapy: the testicular, ovarian, renal, and pituitary extracts.

Spermin, as is well known, is the purest of testicular preparations. Before I had given any attention whatever to these agents, I had submitted evidence<sup>1</sup> which showed that the adrenal secretion was carried to the pulmonary air-cells, to take up the oxygen of the air therein, and become the albuminous (previously unidentified) constituent of the hæmoglobin, which, through the intermediary of the red corpuscles, supplies oxygen to all the tissues. The evidence showed that it was an oxidizing body acting catalytically; that it resisted all temperatures up to, and even, boiling; that it was insoluble in ether and practically insoluble in absolute alcohol, and gave the guaiac, Florence, and other hæmin tests. Now, spermin not only raises the blood-pressure, slows the heart, and produces all other physiological effects peculiar to the adrenal principles, but its solubilities are the same; it gives the same tests; it resists boiling. Moreover, it is regarded in Europe as a powerful "oxidizing tonic" and has been found equally useful in disorders in which adrenal preparations had given good results. The inference that spermin consists mainly of the adrenal product

<sup>1</sup> Sajous: "Internal Secretions and the Principles of Medicine," i, 1903; ii, 1907.

suggests that it should not be regarded as specific to the testes, but, instead, a constituent of the blood at large; not only did this prove to be the case, but it was found in the blood of females as well as in that of males, as we have seen.

As I have also shown in a previous chapter, the dependence of ovarian preparations, including corpus luteum, upon the adrenal principle for their activity is no less evident. Ovarian extract has been found to contain "an oxidizing ferment comparable to spermin."<sup>2</sup> Just as castration causes a decline of the temperature, so does removal of the ovaries; while both spermin and ovarin restore the temperature to normal. This corresponds with the influence on general oxidation I ascribe to the adrenal secretion. As is the case with the latter, ovarian preparations enhance metabolism and the excretion of phosphoric acid. Again, the resemblance of the effects of ovarian preparations to those of adrenal gland is striking. "Fresh ovarian extract," writes Wilcox,<sup>3</sup> "is said, when injected in rabbits, to raise the blood-pressure, diminish the heart's action, and slow the respiration; and when administered to the human female, also to increase the arterial tension. In the castrated animal it is found to increase oxidation to something above the normal degree." Sauvé<sup>3a</sup> states that it increases oxidation and the proportion of hæmoglobin in the blood.

Besides this mutual relationship between the testicular, ovarian and adrenal products, two suggestive facts assert themselves: Not only have Schäfer and others found that a close analogy exists between the interstitial cells of the testicles and ovaries and the cells of the adrenals, but all three sets of organs are derived from the Wolffian body.

The kidneys have been credited with an internal secretion, but no experimental work so far recorded justifies such a conclusion. There is, however (see page 467), testimony to the effect that, as in the organs just referred to, the adrenal principle is the main active agent. Batty Shaw,<sup>4</sup> remarking that the favorable effects obtained from renal extracts are similar to those that "have been reported as a result of treatment by

<sup>2</sup> Batty Shaw: "Organotherapy," 1905.

<sup>3</sup> Wilcox: "Pharmacology and Therapeutics," 7th ed., p. 824, 1907.

<sup>3a</sup> Sauvé: Paris médical, April 1, 1911.

<sup>4</sup> Batty Shaw: *Loc. cit.*, p. 216, 1905.

means of spermin and testicular extract," suggests that "possibly nephrin and other renal preparations provide a means of stimulating oxidation in general, the kidney merely sharing in this oxidation." The concordance of this opinion with my own view (1903), that the adrenal secretion is the constituent of the hæmoglobin molecule which carries on oxidation, is self-evident. The influence of renal extracts on oxidation is further shown by the observations of Brown-Séquard, Teissier, and Fränkel,<sup>5</sup> that they increased the output of urea, phosphates, and uric acid, and by those of Brown-Séquard, Dromain, and de Pradel Bra,<sup>6</sup> Mois,<sup>7</sup> Bitzou,<sup>8</sup> Dubois,<sup>9</sup> and others, which showed that they possessed marked antitoxic power. This also harmonizes with my views, since I have shown, with ample evidence to sustain this assertion, that the adrenal secretion is a basal factor in *all* immunizing processes—as its rôle in oxidation would normally suggest. Even the morbid effects of exaggerated antitoxic activity which I ascribed to excessive doses are exemplified by an observation of Layral's<sup>10</sup> in which renal extract caused death from pernicious anæmia, *i.e.*, from hæmolysis.

Pituitary extracts, we have seen, are active according to which of the two lobes of the pituitary is used to prepare them. Howell, Silvestri, Thaon, and others have found that extracts of the anterior lobe were practically inert, while those of the posterior proved quite active. Howell<sup>11</sup> states in this connection that they "cause a marked rise of blood-pressure and slowing of the heart-beat," remarking, moreover, that "these effects resemble in general those obtained from adrenal extracts, but differ in some details." When we take into account the wealth of this organ in nervous elements, deviations in minor effects are readily accounted for.

As previously stated, the adrenal principle is not destroyed by boiling. This was also observed to be the case with extracts of the pituitary lobe, by Schäfer and Herring.<sup>12</sup> These physiologists also noted that they produced dilatation of the renal

<sup>5</sup> Teissier and Frankel: Lyon médical, April 29, 1894.

<sup>6</sup> Bra: Comptes-rendus de la Société de Biologie, July 26, 1895.

<sup>7</sup> Mois: Clinica Moderna, Dec. 1, 1897.

<sup>8</sup> Bitzou: Journal de physiologie et de pathologie générale, Nov. 15, 1901.

<sup>9</sup> Dubois: Bulletin général de thérapeutique médicale et chirurgicale.

<sup>10</sup> Layral: Bulletin médical, Oct. 8, 1898.

<sup>11</sup> Howell: *Loc. cit.*, 2d ed., p. 802, 1907.

<sup>12</sup> Schäfer and Herring: Transactions of the Royal Society, exlix, p. 1, 1906.

vessels, but this is a normal result of the vasoconstriction produced by them in the body at large, owing to the action of the adrenal principle upon the vascular muscles. The renal capillaries, in keeping with all others, being deprived of muscular elements, they are passively dilated by the blood compressed out, as it were, of the larger vessels and the kidneys are dilated.

Herring,<sup>13</sup> and more recently McCord,<sup>13a</sup> noted that pituitary extract caused constriction of the peripheral arterioles. This is typical, as is well known, of the action of all adrenal products. As shown by the experiments of Garnier and Thaon,<sup>14</sup> Conti and Curti,<sup>15</sup> and others, the pressor precede the depressor effects. This applies as well to the inhibitory effects on the pancreas recently recorded by Pemberton and Sweet.<sup>16</sup> The mydriatic action of epinephrin, discovered by Meltzer, has also been found by Cramer to apply to pituitary extract. Finally, the clinical effects recorded, especially those on the cardiac disorders by Cyon, Rénon and Delille,<sup>17</sup> clearly indicate that they are due to the adrenal principle pituitary extracts contain. Both are extolled as oxytocics, being deemed far superior to ergot by some. Both also have been found very effective in intestinal paresis. The resemblance of their action to that of adrenal extracts, noted by Schäfer, is explained, therefore; it is to the adrenal principle in the pituitary that extracts of this organ owe their activity. Finally, as shown by Wiesel,<sup>18</sup> the pituitary body is the seat of a large group of chromaffin cells, *i.e.*, adrenal cells. Recently Watanabe and Crawford<sup>18a</sup> found that pituitary extracts contained "an epinephrin-like compound."

All the facts seem to me to justify the inclusion of testicular, ovarian, renal, and pituitary extracts in the adrenal group of organic extracts.

I would add that the presence of the adrenal principle throughout the organism is no longer to be doubted. Besides its now-familiar effects on the blood-pressure by a direct action on the blood-vessels, which necessitates its distribution broadcast,

<sup>13</sup> Herring: Journal of Physiology, Nov. 2, 1904.

<sup>13a</sup> McCord: Archives of Int. Med., Nov. 15, 1911.

<sup>14</sup> Garnier and Thaon: Jour. de phys. et de path. gén., March, 1906.

<sup>15</sup> Conti and Curti: Bollettino delle scienze mediche, Nov., 1906.

<sup>16</sup> Pemberton and Sweet: Archives of Internal Medicine, July, 1908.

<sup>17</sup> Rénon and Delille: Journal des praticiens, No. 42, 1907.

<sup>18</sup> Wiesel: International Clinics, vol. ii, 15th series, 1905.

<sup>18a</sup> Watanabe and Crawford: Jour. of Pharmacol. and Exp. Ther., Jan., 1916.

we have the fact that Mulon found it in the red corpuscles. Even the placental blood contains it. As a conservative pharmacologist, Dixon,<sup>19</sup> wrote, while describing investigations by F. Taylor and himself: "We have shown that the human placenta contains a considerable amount of a substance which is . . . unaffected by boiling. This body has the property of powerfully constricting blood-vessels, of contracting the uterine muscle, of raising the blood-pressure. . . . So far as we have been able to determine, this body has all the properties of adrenalin." Indeed, "adrenalinemia" is now in common use.

The adrenal principle being common to the entire organism, it would seem as if all organic extracts should owe their therapeutic activity to this constituent. But many facts go to show that the proportion of adrenal principle in certain organs—those forming part of the chromaffin system, for example—is far greater than in others, and moreover that they contain cellular elements that are not only similar to the secreting elements of the adrenals, but which are capable of adding to that received from the latter through the blood. This accounts for the fact that removal of the testicles or ovaries lowers the activity of the oxidation processes, though without destroying life itself, as is the case when the adrenals are removed. The obesity which follows removal of the testicles or the ovaries illustrates an effect of this suboxidation.

This does not mean, however, that all organic preparations owe what therapeutic efficiency they have shown mainly to the adrenal principle they contain. The majority of them probably do not. The recent introduction of an oily extract of brain matter seems to have placed the use of this agent on a firmer basis. The phosphorus-laden nucleins derived from brain substance would probably account for what therapeutic value it seems to show. Again, thymus extract has some claim to recognition in disorders which other remedies do not seem to affect. Here again, we have a tissue rich in nuclein, and therefore in phosphorus. May we not have in these and other organic preparations a means of introducing into the body phosphorus so bound up in organic combination that it can be far more readily taken up by our tissues than any prepara-

<sup>19</sup> Dixon: British Medical Journal, Sept. 21, 1907.

tion that our laboratories can produce? We must not lose sight of the fact that organotherapy affords, precisely in this direction, possibilities that nothing else in the realm of therapeutics can offer—a statement which applies also to the opportunity they furnish of introducing immunizing bodies directly into the blood—or of compensating for organs whose functions have become inadequate through local disease. But these advantages will only become available when the prevailing empirical use of animal extracts will have been rendered impossible through proper identification of those of their constituents which bring about beneficial effects, the natural precursor to a clear conception of their mode of action.

Another important feature is the distinction of true ductless glands, whose mission is to elaborate a secretion of physiological use to the body at large, from organs which have been credited with such functions on insufficient grounds. Perhaps the habit of requiring considerable evidence from many sources and directions before reaching a conclusion—contrary to the prevailing tendency among experimenters to base a sweeping conclusion upon very few facts—has rendered me too exacting, but I must confess that so far I have not been able to recognize *true* internal secretions in more than three sets of organs, the thyroid, including its glandules, the parathyroids, the adrenals, and the pancreas. In these organs alone has the secretion been identified at the seat of its formation, traced to the bloodstream, and, through the blood, to all tissues. This might be said to apply to the liver, owing to its glycogenic function and to the broadcast distribution of glycogen; but in accord with Claude Bernard's original view, physiologists very properly consider the formation of glycogen as "a temporary reserve supply of carbohydrate material that is laid up in the liver during digestion and is gradually made use of in the intervals between meals."<sup>20</sup> Glycogen, therefore, is not a true internal secretion.

Many other organs have been regarded as sources of internal secretions. A close analysis of the question, however, suggests that while the evidence in favor of this view is very meager, many facts tend to disprove it. Investigators who have contended that these and other structures are ductless glands have,

<sup>20</sup> Howell: "Textbook of Physiology," p. 735, 1905.

almost without exception, based their contention on the plea that extracts of these structures produce physiological effects. This accounts for the fact that practically every tissue, including muscles, nerves, lymphatic glands, and even ciliary body, nasal mucous membrane, the placenta, has been thought to produce an internal secretion. The weakness of such a plea is self-evident. Almost any organic substance will in some way or other affect the blood-pressure, and when we consider that all tissues contain more or less nuclein, intermediate, and therefore toxic, waste products, red and white corpuscles, and many other substances capable each in its own way of evoking some sort of reaction when injected into animals, the actual value of such experiments is reduced to *nil*. It is about as scientific as the giving of hashed ear for earache.

Finally, and quite in keeping with the above remarks, is that those of the organic products which are to any degree toxic may, through the adrenal system, evoke an auto-protective reaction the symptoms of which seem to the investigator the expression of a physiological function which he credits to the extract used, supposedly an "internal secretion." On the other hand, beneficial effects are sometimes obtained through the fact that certain tissues combine the properties of two or more internal secretions, the posterior pituitary lobe, for instance, which is rich not only in chromaffin or adrenal substance, as stated, but also in nucleins, owing to its wealth in nervous elements.

Some of these physiological effects will be brought out under the remaining headings of this chapter.

#### THYROID ORGANOTHERAPY.

When, in the light of the data submitted in the third chapter, we administered thyroid gland, which combines the actions of the thyroid and parathyroids, the following effects are produced: It renders the phosphorus of all tissues, and all free substances, such as bacteria, wastes, toxins, etc., containing phosphorus, more inflammable or sensitive to the action of the oxygen in the blood. As this applies particularly to nerves and nerve-centers (all of which are especially rich in phosphorus) the adrenal center and therefore the adrenals themselves are excited, and, the

adrenal secretion being the agent which takes up the oxygen of the air to sustain the blood's oxygenizing power, the supply of oxygen is also increased. All the various phosphorus-laden substances are thus not only rendered more readily oxidizable by thyroid extract, but this remedy also provides indirectly the required oxygen. This is not all, however. As the functions of all organs are enhanced by this process, the pancreas and the leucocytogenic organs are also stimulated, and trypsin and phagocytes, which are the active destroyers of pathogenic organisms, toxins, and other poisons, are also increased. Briefly, under the influence of thyroid preparations, we have in the blood—and demonstrable therein—all the active agents concerned with *metabolism*, *nutrition*, and *immunity*: an increase (1) of adrenal oxidizing substance, or adrenoxidase (the albuminous constituent of hæmoglobin; Ehrlich's amboceptor); (2) of thyroid sensitizing substance (Wright's opsonin); (3) of trypsin (Ehrlich's complement and Metchnikoff's cytase) and (4) bacteriolytic leucocytes (Metchnikoff's phagocytes).

When, therefore, thyroid preparations are given in small doses, we may expect the following phenomena, especially when the remedy is given in cases of hypothyroidia:—

A *rise of temperature* due to the increased oxidation brought about by the thyroid and adrenal oxidizing substances acting jointly; *enhanced metabolism* a normal result of the augmentation of general oxidation, with *increased appetite* due to the resulting greater demand for foodstuffs. A marked improvement in *general nutrition* and *strength* is a self-evident result of the assimilation of a greater proportion of food-materials, and the *rapid growth* likewise where, as in cretinism, it is stunted. The *cerebro-spinal system* is particularly influenced owing to its wealth in phosphorus; there is, in suitable cases, *development of intelligence*. All organs being the seat of increased metabolic activity and nutrition, the intestinal, renal, cardiac, and cutaneous and hepatic functions are all enhanced. Even the hair grows bountifully not only in cretinism, but when its loss is due to impaired nutrition of thyroid origin. It counteracts *premature senility* in all its phases by restoring to the organism the main constituent which sustains, with the co-operation of the adrenoxidase, the functional efficiency of all its parts.

In large doses, on the other hand, thyroid preparations produce quite the opposite effects. By imposing hyperoxidation upon all cells, these are catabolized or broken down before they can be adequately built up, *i.e.*, anabolized, and, instead of increased nutrition, we behold gradual emaciation beginning with the adipose tissues, which are the first to succumb. Hence the use of thyroid preparations in obesity.

Small doses are, therefore, indicated in all cases to begin with, 1 grain (0.066 Gm.) of the desiccated thyroid in adults, for example, and  $\frac{1}{2}$  grain (0.033 Gm.) in children over 2 years old. Gradually, the dose may then be increased, remembering that 3 grains (0.2 Gm.) three times daily should not be exceeded—notwithstanding the “average dose” of 4 grains (0.26 Gm.) given in the U. S. P., which is excessive. A milk-sugar triturate termed *iodothylin*, though not as active as the above, is more suitable for little children in 1- to 5-grain doses.

When thyroid preparations are judiciously used, that is to say, when their action is controlled by giving only carefully adjusted doses, aided by the concomitant use, if needed, of other agents—iron, for example—to supply the hæmatin necessary to build up the hæmoglobin molecule; when also with thyroid we wish to increase the albuminous moiety of that molecule, strychnine when the blood-pressure is too low to insure adequate tissue nutrition, etc., results are obtained which soon convince the clinician that they constitute a very valuable addition to our armamentarium. Especially does this obtain:—

1. In diseases due to slowed destruction of toxic wastes, as shown by its action in tetany, epilepsy, eclampsia, disorders of menopause, asthma, chronic rheumatism, migraine, and also by those due to slow oxidation of fats, as in obesity.

2. In diseases due to lowered general nutrition of all tissues, including the bones, as shown by its action in hypothyroidia, cretinism, myxœdema, and kindred disorders in which calcium metabolism obtains—osteomalacia, rickets, and osteomyelitis.

3. In disorders due to lowered nutrition of the muscular elements, including the skeletal and vascular muscles, as shown by its action in general adynamia, neurasthenia, and myasthenia.

4. In all cases in which the processes of repair or absorption are deficient, as shown by its action in delayed union of frac-

tures, certain benign and malignant neoplasms, and syphilitic tissue and bone necrosis.

5. In infectious diseases—owing to the increase of auto-antitoxin, thyroiodase (opsonin), and phagocytes—as shown by its action in the early stages of tuberculosis, typhoid fever, infectious tonsillitis, and certain exanthemata.

The majority of the disorders enumerated above, apart from those already reviewed, will be found treated at length in the second volume. In the following pages, however, I will include only those conditions which in addition to those studied in the third, fourth, and fifth chapters of the present volume, and in the second volume, are of special practical importance as a field for thyroid organotherapy.

INSANITY.—What data we possess on the relations between mental disorders and the thyroid apparatus indicate that both hypothyroidia and hyperthyroidia are equally fruitful in the genesis of many psychoses. Could we clearly establish a line of demarkation between these two states, however, their study would present no difficulty; but such is not the case in the light of prevailing views. Thus the classic symptoms of myxœdema may be accompanied, especially in the advanced stage, by mental disorders which are not in keeping with the asthenic phenomena that belong to hypothyroidia. The report of the Committee of the Clinical Society of London showed, for instance, that, while a certain proportion of cases of myxœdema suffered from melancholia, the one mental disorder we should expect to find in such a depressive state of the thyroid apparatus, the majority suffered from dementia, acute and chronic mania, delusions, and hallucinations, all of which denote some degree of functional erethism.

Nor do we obtain aid through the morbid histology of the thyroid in insane cases. As stated by Ramadier and Marchand,<sup>1</sup> after an examination of 278 thyroid glands of patients who had died in four different asylums, it is impossible to establish any constant relation between the thyroid changes and the form of mental disease from which the patient suffered.

Yet, there is much to be discerned and there are many therapeutic hints to be garnered when these cases are interpreted

<sup>1</sup> Ramadier and Marchand: *L'Encéphale*, Aug., 1908.