THE ORGANS OF INTERNAL SECRETION

THE ORGANS OF INTERNAL SECRETION

THEIR DISEASES AND THERAPEUTIC APPLICATION

A BOOK FOR GENERAL PRACTITIONERS

BY

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To

MY FATHER

IN TOKEN OF LOVE AND RESPECT

PREFACE TO THIRD EDITION

In this edition several important alterations have been made in the construction of the book. A chapter has been inserted dealing with the physiology of the Internal Secretions and their inter-relationships, as it has been felt that a chapter on this subject would be helpful as an introduction to the study of the individual glands. The position of this chapter has necessitated the renumbering of the subsequent chapters; and two chapters have been added in later parts of the book. Chapter XI. deals with the inter-relationship of the ductless glands and the nervous system, and forms an introduction to the following chapter, which remains unchanged from the Second Edition. Chapter XIV. discusses some practical points in hormone-therapy, and continues the material under consideration in the preceding chapter.

Several parts of the book have been largely re-written, and additions have been made in various places. The majority of these deal with data which has recently been published, and it is hoped that their addition will bring the work thoroughly up to date.

Queen Anne Street, W.,
August, 1921.

PREFACE TO SECOND EDITION

The fact that a Second Edition of this book has been called for a little over a year after publication appears to indicate that it has fulfilled a want. The need of a small work dealing with the Internal Secretions has apparently been felt, not only in this country, but in others, as was shown by a demand for an edition in Spanish and another in Italian.

The entire book has been carefully revised and brought up to date. Numerous references have been added, and a chapter dealing with the Relation of the Internal Secretions to Functional Nervous Disease has been inserted. The desirability of a chapter discussing this relation had previously been brought home to the author; but the large increase in these disorders in the last year or two has made such an addition imperative.

Chapter XI. contains a brief review of this subject. Chapter XII. is devoted to a survey of the whole subject, and, except for several additions to the

Bibliography, remains unchanged. A list of some books dealing with the subject of Functional Nervous Disorders has been added.

The author desires to express his thanks to Dr. Bernard Hart for much help in the classification and nomenclature of these disorders.

BRINNINGTON WAR HOSPITAL,
STOCKPORT,
September, 1918.

PREFACE TO FIRST EDITION

This book is founded upon articles which appeared in the *Medical Press and Circular* during the summer and autumn of 1916. The author's object in writing these articles was to lay before the busy practitioner the important points in the study of the Endocrine Glands. At the same time he was anxious to make them as complete as possible, and yet keep them within the limits of such publications.

After the appearance of these articles, he received requests for reprints, and as they had not been reprinted, and the interest in them appeared to warrant it, he decided to publish them in book form. The present volume comprises these articles, with slight alterations.

Hormone-therapy is already established as a recognized therapeutic agent, yet as the books which deal with the ductless glands and their secretions are exhaustive studies including the results of laboratory research in detail, and require far more time to read than the general practitioner has at his disposal, it is difficult for him to glean the salient facts from these lengthy works. It seemed, therefore, to the author that a small book which contained an account of the diseases and therapeutic application of extracts of these glands might prove useful.

In publishing this small volume, however, the author wishes to state that it makes no claim to be considered an exhaustive and complete account of the endocrine glands, neither can it be considered as a comprehensive therapeutic guide to the administration of the organic extracts. Rather does it aim at being a guide to other practitioners as to the rôle which the ductless glands play in promoting bodily health; while it endeavours to point out those morbid states of health in which organic extracts may be utilized with success.

Among the glands possessing an internal secretion, the thyroid is perhaps the one which has attracted most attention, partly on account of the well-recognized disorders which arise in connection with it, and partly because, of all the endocrine glands, the thyroid has been most utilized therapeutically. In order to emphasize the signs and symptoms associated with morbid conditions of this gland, the author has devoted three chapters to the consideration of Exophthalmic Goitre and Thyroid Deficiency. The last of these three chapters contains references to the administration of thyroid extract; while this subject is again referred to in Chapter X.

A chapter has been devoted to the Pituitary Gland, and the subject of pituitary-therapy has been briefly reviewed. In Chapter VI. the Adrenal Glands are described, and the clinical conditions of hyperadrenia and hypoadrenia are discussed. Chapter VII. deals with the Pancreas, and describes its structure, physiological functions, and relation to glycosuria, and concludes by referring to the therapeutic possibilities of preparations of this gland.

The subject of the Internal Secretions of the Sexual Organs, dealt with in Chapter VIII., has been compressed into as small a space as was possible; a full account would have filled a large volume. Nevertheless, this chapter reviews the outstanding features, suggests ways of administering extracts of the genital glands, and describes morbid conditions in which they may be helpful.

The Internal Secretions of Digestion form the subject of Chapter IX.; and here the author has endeavoured to lay emphasis upon the therapeutic aspect, as he believes that in the near future this branch of organo-therapy will find a very wide field of utility, and will succeed in alleviating many morbid conditions which have hitherto proved resistant to treatment.

The Therapeutic Application of Hormones is summarized in Chapter X. This chapter has been enlarged since its appearance in the *Medical Press and Circular*, and it endeavours to epitomize the subject for those readers who are mainly concerned with the therapeutic aspect of this subject. It necessarily summarizes the conclusion of each chapter, but in addition references will be found to preparations and doses not included in the previous chapters.

Chapter XI. is devoted to a survey of the whole subject, and deals with the present position of hormone-therapy.

As the therapeutic aspect of this subject was dealt with at the end of each article, it has been decided to leave this arrangement unaltered. Likewise, the references have been left in their original positions; but a bibliography has been included at the end of Chapter XI., so that those desirous of a fuller account of the ductless glands and organo-therapy will be able to refer to the works enumerated there.

In conclusion, the author desires to thank the editor and proprietors of the *Medical Press and Circular* for permission to reproduce these articles in book form.

IVO GEIKIE COBB.

SEYMOUR STREET, W.,
November, 1916.

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INTRODUCTION

The place which those glands possessing internal secretions now occupy in the practice of medicine cannot be over-estimated. Although it is only in recent years that their importance has been understood, every day brings to our knowledge fresh evidence of their vital influences upon the general bodily and mental health. When it was discovered that exophthalmic goitre is always associated with over-action and hypersecretion of the thyroid gland, the first milestone had been passed in the path which led us to the discovery of the important part which the hormones play in our lives.

What we may call the grosser lesions due to disturbances in the normal ratio between the various internal secretory glands are nowadays matters of almost popular knowledge. What we desire to emphasize in this book are the smaller signs and symptoms which, to the eye trained to observe, show minor disturbances, either of one or more glands or of the balance between these glands. Many of these details, trifling in themselves, have been proved to be sufficiently characteristic to justify medical science in including them among the constant features which owe their origin to the ductless glands. When the pioneer work was being done on this subject, the evidences of the slighter disturbances of the endocrine glands were regarded by many observers as too fanciful to merit serious consideration. Thus, when Levi and Rothschild first pointed to the "eyebrow" sign as indicative of deficient thyroidism, it was hard for many students of these subjects to convince themselves that this sign was of any value whatsoever.

Nevertheless, this and other manifestations of equally slight nature are now admitted to be of the greatest value in diagnosing deficient thyroid secretion. Many of the signs of kindred nature are so slender as to require the most minute study and the most careful observation before we can say, with any degree of probability, which particular gland is at fault. The importance of this lies in the fact that many cases of "functional disturbances," which we have been content previously to cosset with various preparations, and to class as neurotic or neurasthenic according to the depths of our ignorance, are now recognized as originating in abnormal functioning of the endocrinic glands. This much is now generally known and universally admitted. Only relatively few observers recognize that this is not the *fons et origo mali,* but only one stage on the journey.

The prevalence of infections of various kinds, and the frequency with which an individual living under modern conditions succumbs to a "chill" or other disorder not definitely diagnosed, are factors which have to be reckoned with when considering the etiology of endocrinic disturbances. The part which mental strain plays in upsetting the bodily harmony has been proved beyond doubt by the war. There were countless examples of hyperthyroidism or hyperadrenia (to mention the types most easily recognizable) met with supervening upon psychical trauma. These were cases which had been submitted to sudden and violent mental shock, in many instances supervening upon previous prolonged mental strain.

It is justifiable to assume that the strain inseparable from modern civilian life is likewise able to produce endocrine disturbance, although the cause is usually of longer standing. Many patients suffering from the neuroses, as well as certain vague metabolic disturbances, are now beginning to sort themselves into categories quite different from those previously recognized.

To take a concrete instance, let us suppose that a patient exhibits signs that the thyroid is not functioning adequately. The patient exhibits many of the well-known signs pointing to this deficiency. Most of us are well content to leave it at that, and even to spend time (which should be occupied in delving still farther and asking ourselves why such a deficiency is present) on self-adulation at our extraordinary deductive powers. It is certainly true that we can benefit our patients by the exhibition of one or other of the organo-therapeutic products, but we shall do so to a much larger extent if we realize one or two simple facts.

When advising a patient to take, let us say, thyroid extract for a time, we are constantly asked by the patient the *rationale* of such a prescription. Having explained that we have reason to believe that this gland is not supplying an adequate amount of secretion, on more than one occasion we have been asked by the logical patient, "Have I got to continue this medicine for the rest of my life?" or, "Will the need for its administration be overcome in due time?" This is an important matter, because it makes us think for ourselves, and not blindly prescribe drugs for indefinite times without reasoning as to their method and length of administration.

I think that we are justified in considering for a few moments what underlies the deficiency in secretion. It is highly improbable that one or other of the endocrinic glands would suddenly and without any stimulus refrain from supplying, or determine to over-supply, its valuable contents to the blood-stream. It is much more probable that some cause, be it mental or bodily, has determined this upset, and it behoves us to realize that this is the case, and not to consider our diagnosis completed when we have made up our mind that such and such a gland is defective or over-active.

In his book on "Intestinal Stasis," Lane states that one of the effects of intestinal intoxication is atrophy of the thyroid. Here we have a definite attempt to go to the root of the trouble, and evidence is accumulating to show that endocrine disturbances are frequently associated with alimentary toxæmia. For the present, at any rate, let us assume that this is one of the causes which underlie submyxœdema. What others may there possibly be? Among the causes of diabetes which find their place in most current textbooks on medicine is worry and anxiety. Now, this is at once assuming that mental causes may upset a bodily function or functions, and thereby disorganize metabolism. And the writer would be the last to wish to deny this. If, therefore, we may assent to this detail of etiology with regard to diabetes, why should we not include such a cause when we are discussing disorganization of the endocrinic glands? Many cases which we can call to mind at the moment afford us the strongest possible support for such a theory. Prolonged anxiety, business worry, a sudden shock, are said to be capable of producing diabetes, just as puncture of the floor of the fourth ventricle is, experimentally, capable of doing the same. It would seem at least equally probable that the same causes can, and do, upset the mechanism which governs the balance between the ductless glands.

In the severe cases of this nature (*e.g.*, Graves' disease), this fact is sufficiently recognized. But is it, has it been, when we come to consider slighter derangements of these important glands? It is obvious that the entire study of this subject is of too recent a date to have made the minute clinical study of the ultimate cause a feasible proposition. Nevertheless, we now come to the time when our patients ask us the why and the wherefore of such prescribing.

We have suggested two possible causes which may underlie the disorganization of the endocrinic system—namely, intestinal toxæmia (as suggested by Lane); and mental causes, such as worry, anxiety, and mental strain of any kind. But are these the sole causes which may be held responsible? We are all familiar with the damaged health which may result from a long illness, or, alternatively, from a sudden short attack, such as influenza. The patient recovers but slowly, the strength returns not, the mind is clouded, and in countless other ways the individual shows the effects of the illness. Hitherto we have referred to such cases as post-influenzal debility, when this disease has been at the root of the trouble; or as "neurasthenia," when we could not find a cause even as tangible as influenza. Our remedies have been confined, certainly in many instances, to a change to the sea or spa, and a generous addition to the diet. But we have rarely asked ourselves what factor underlies these "delayed recoveries."

Why should not the toxins of influenza, in like manner to the toxins generated by the inhabitants of the bowel, or the adverse mental influences which exert their harmful action where mental strain is present, be capable of producing an endocrinic disorganization? Hypothetically, at any rate, such an occurrence is at least probable, and it would give us a reason for the sudden or gradual withdrawal of the internal secretion which happens to be deficient in the particular case.*

From the practical standpoint, moreover, we must advance some such hypothesis as this in order to account for the train of symptoms, which, certainly in many cases, owes its origin to a disturbance of the normal ratio which exists in health between the various endocrinic glands. Again, most of us are familiar with the cases of delayed convalescence following an operation. The patient invariably presents a similar picture to that designated "post-influenzal debility." In theory, at any rate, he ought to respond to the administration of one or other of the preparations of the hormones, and in many cases he does.

On more than one occasion I have had the opportunity of putting this theory into practice. One lady consulted me some years ago for neurasthenia following a severe abdominal operation. This condition had resisted a wealth of treatment; many and diverse remedies had been tried without relief. I hoped that I might be enabled to afford relief by the administration of an organo-therapeutic preparation. On considering her syndrome, I came to the conclusion

* It has recently been reported in the Archives of International Medicine, that a series of experiments have led some American investigators to the belief that progressive muscular dystrophy may originate in a disturbed functioning of the endocrine glands.

that she might derive benefit from the exhibition of pituitary extract. In spite of the laboratory evidence, which should convince us that it is useless to give an extract of this gland by the mouth, I took my courage in both hands and prescribed it. The result surpassed even my optimistic expectations. The lady recovered her strength and health; her digestion righted itself; her functions became normal, and she regained perfect health. This result is striking, for it followed many other remedies, and the patient herself always refers to this medicine as the "magic mixture."

I mention this case as it exemplifies our hypothesis that many and diverse causes may produce a change in the normal functioning of these glands. Whether, in this particular case, it was the shock of the operation, the anæsthetic, or the changes in diet necessitated by these procedures, it is impossible to say. An example of a similar attack of "thyroid deficiency" is the case of a lady who, having nursed her husband through a long and trying illness, which resulted fatally, consulted me for symptoms which, upon investigation, were shown to be due to deficient thyroid secretion. Upon the administration of thyroid extract, she made a capital recovery and was restored to health.*

* The field of utility of thyroid extract is widening rapidly as fresh knowledge is gained as to the various diseases in which disturbance of the thyroid plays a part. As an example, its action as a diuretic, and the use to which this can be put in metabolic disorders, has earned for it the name "physiological digitalis."

These cases both help us to answer the question so often put to us when we recommend an extract of one or other of these ductless glands. It would seem that, certainly in many instances, the administration of the extract either by the mouth or hypodermically serves to act as a stimulus to the normal secretion, so that it is unnecessary to continue artificially its administration for lengthy periods. And, again, the prescribing of the requisite extract at the right time is the "shortest cut" to health which exists.

It is even possible that many of the benefits which we all recognize to accrue from a change of climate, from a course of spa treatment, or from a sea-voyage, are really largely efficacious because they stimulate into activity the gland (or glands) which has been temporarily inhibited by the illness, operation, or other cause. In this connection reference may be made to another instance where "post-influenzal debility" has yielded to organo-therapy. A lady consulted me for this condition, which had been in existence for five years, and which had resisted all treatment. It had commenced after a bad attack of influenza five years before. Her condition was much improved from the first by the administration of thyroid extract, and she made a most satisfactory recovery.

The point which seems to need emphasizing is this: that prolonged illness, shock, mental anxiety, and many other causes, produce effects which owe their origin to a disturbance of the relation between the hormones. The indications are rarely broad. Sometimes they require the eye of a medical "detective" before their significance is realized. But the signs and symptoms are rarely wanting if they are looked for.

Neurasthenia has been likened to influenza (inasmuch as any intangible condition has received this label), and has been dubbed the "dustbin of the neurologist." Nevertheless it is a real and concrete disease—concrete in the sense that it is not a hotchpotch of other diseases. Doubtless some of the diagnoses which have been made under this name would in reality have received another title did we but realize what was the underlying pathology. Some patients who have been called neurasthenics are in reality neurasthenics, but they are neurasthenics because they are suffering from a deficiency of hormones.

I may perhaps be allowed to mention one other case as illustrating the relation between neurasthenia and the endocrinic glands. During the course of last year I was consulted by a doctor who informed me that he was a neurasthenic, and brought me a typewritten account of his symptoms, in support of this statement. I need not describe the case in detail, as the few points I mention will serve our purpose.

The patient complained that he was slow mentally, became extremely tired after comparatively small exertion, was exhausted after sexual connection, unable to concentrate for any length of time, and so on. On examination, I discovered a very slow pulse (barely fifty to the minute), a dry and rough skin, prematurely grey hair, especially over the temples (the patient was in the thirties), trophic changes in the skin appendages, and many other minor signs which I will not waste time by enumerating. Suffice it to say that the patient presented a typical picture of submyxœdema, and I advised small doses of thyroid. Some months later he advised me that he had suffered from some "extraordinary sinking feelings" when he had taken the thyroid, and in consequence had been forced to abandon it. I explained that these were most certainly due to the stimulating effect which the thyroid would produce upon the circulation, and I encouraged him to persevere with it. The interest of this case lies in the fact that all the symptoms had gradually supervened after an attack of influenza, and that their real nature had never been diagnosed.

Such a case as this will serve to show how a certain proportion of patients who have been treated, and only too frequently dismissed as incurable under some such name as neurasthenia, may be helped by the judicious administration of these extracts.

I need not offer an account of the symptoms which make up these diseases, nor is there need for me to describe in detail what is so well known about individual symptoms of deficiency in thyroid, in pituitary, or in adrenals. But one or two points have come to my notice about these conditions that I should like to mention in passing.

There can be little doubt that deficiency in thyroid secretion comes on more or less suddenly in some cases. I recall the case of a young male subject who developed this complaint after a hazardous season on the Stock Exchange. His condition, when he came under my observation, was typical, and he made speedy progress under thyroid medication. Again, I have seen a typical attack of submyxœdema develop after one of the exanthemata; likewise excessive thyroid secretion ensues after such a disease as rheumatism.

It may be of interest to note at this place the extraordinary intolerance to tobacco which develops when the thyroid secretion is deficient. I have on several occasions observed that the patient, a heavy smoker previously, has had to abandon the fragrant weed at or about the time when his illness commenced. I have been told that even one cigarette is followed by unpleasant sensations, and I have ascertained that the blood-pressure has been lowered as much as ten points after one cigarette.

These occurrences all point to the fact that, given suitable conditions, it is not a difficult matter to upset the normal ratio between the various hormones. It is necessary in these cases to study the antecedent conditions with as much care as we should when taking the previous history of, let us say, a case of tuberculosis. For in these patients we can often discover some occurrence which may well have some bearing upon the etiology, and may give us valuable information both as to the actual cause and as to the particular gland at fault.

Unfortunately, the therapeutics of the other glands are scarcely in such a satisfactory state as that of the thyroid gland, and we do not, in practice, obtain results as striking as those which so often ensue from the administration of thyroid. But, before leaving the subject, we may say a few words as to the prescribing of the adrenals.

The extract of the adrenals may be given in the form of dry extract, and it is often of great benefit to those patients who are weakly, debilitated, with a low blood-pressure and constant fatigue. These are the cases of neurasthenia in which this extract should be tried. Again, the preparations of one or other part of the pituitary gland are in some of these cases more beneficial; while it is sometimes of service to use what Leonard Williams calls a "mitrailleuse" —*i.e.*, a preparation containing the extracts of many glands. Such a one is Hormotone, and it is claimed that its exhibition is followed by marked benefit in many indefinite conditions.

The method of treating disease by means of extracts of the endocrinic glands is, relatively, still in its infancy, so we must not be hypercritical at that part of this medication which works without the support of the laboratory. But, as has been admitted elsewhere by a physiological chemist, clinical experience often is at variance with laboratory results, and clinical results are not always in the wrong. However much we may condemn the indiscriminate and speculative use of these extracts without adequate reasoning, if we abide by laboratory results, and never test these by practical endeavour, we are liable to remain with little added knowledge on these subjects as the years roll on.

The practitioner must perforce use his eyes before he prescribes thyroid extract; he must be familiar with the small signs which go to make up the picture of deficient or excessive action of this gland; and he must not hesitate to prescribe this substance, although the signs are slight. He must be familiar with the diagnostic features, and he must be equally *au fait* with what is now known about treatment. He must choose a carefully standardized preparation; be careful that his preparation is new, and not several months older than when the local chemist purchased it from the wholesale house; and, finally, he must understand that the dose is a matter deserving the closest attention. Thyroid, to quote one example, is not a drug to use from 3 to 10 grains, but in fractions of a grain—certainly to commence with. Had it not been for the fact that it has been utilized to reduce weight, the probability is that it would not have obtained that popularity which it now possesses in the lay mind. This has made its administration a matter of danger, especially when we consider that the dose, or rather the initial dose, is often far too large.

Convalescence is frequently accompanied by deficiency in the thyroid gland, and its administration in minimal doses is of very real help. During the months which follow a serious illness, such as pneumonia, the administration of a " mitrailleuse " is frequently indicated. The tendency to obesity, or alternatively to undue loss of flesh, which is usual after severe illnesses, would point to an upset in the hormone balance; and this may be remedied by a careful study of the symptom-complex and the prescription of a suitable organo-therapeutic extract.

To all those who treat neurasthenia, who have to lighten the lot of those unfortunate sufferers from what are known as " the functional neuroses," the importance of organo-therapy cannot well be over-estimated. When administered with intelligence, with the patient under observation, there need be no risk in such prescribing. Rather is there a risk in prolonging a morbid condition owing to neglect in the faculty of observation or an oversight as to the underlying causation.

Again, what a difficult matter it is to " fatten up " some patients. Rest cures, hyperalimentation, malt extracts, digestive ferments—all seem to be of no avail. But the extracts of the ductless glands will often be found of service, when taken with regularity. It should, however, be remembered that thyroid must be prescribed with great care in such cases as these. Extracts of the brain and spinal cord, of the pancreas and liver, of the testes and seminal vesicles, are of much help. I have recently had under my care a man suffering from advanced neurasthenia, whose weight had dropped from eleven stone to between eight and nine. Under the administration of a mixed extract his weight is now (one month after the commencement of treatment) nearly ten and a half stone, although nothing had previously been able to stop the loss of weight.

In the *Practitioner* for January and February, 1915, will be found many able articles from the pens of experts on the subject of the endocrine glands. These articles discuss fully the available material both from the standpoint of the laboratory and the bedside. A perusal of these numbers will well repay the time occupied.

To obtain the best results from the therapeutic standpoint, however, a knowledge of the physiology of the Internal Secretions is absolutely essential. The following chapter attempts to summarize this aspect of the subject.

CHAPTER I

THE PHYSIOLOGY OF THE INTERNAL SECRETIONS

Introduction.

THE discovery that the metabolism of the body can be affected by the administration of preparations of organs has led to the establishment of a new branch of therapeutics—namely, organo-therapy. Not that this method of treatment is entirely new; indeed, the employment of animal extracts empirically is exceedingly old; but such treatment has always been based upon a kind of homœopathic reasoning and not upon the physiological knowledge which is now at the disposal of the clinician.

The point of importance in the study of the Internal Secretions is that blood flowing through an organ can acquire characteristics due to the influence exerted by that organ. While, therefore, the phrase "ductless glands" is often understood to mean definite bodies, such as the thyroid, suprarenal, and thymus, the phrase "organs of internal secretion" connotes those structures which secrete a substance influencing or modifying the blood in its passage through the organ. The importance of the blood-stream has been recognized since the time of Harvey; and that it could be the channel through which diseases could be conveyed was naturally the next step. Further researches have only emphasized the fact that it is to the composition of the blood, and to the changes it undergoes under varying conditions, we must look for the pathogenesis of many diseases. The nervous system as a means of transmitting messages is a late development in evolution; the humoral channel is a much earlier arrival. Primitive life responds to chemical stimuli, which are slow in their action, and these have been superseded, so far as speed is concerned, by the nervous system, much as the horse has been superseded by the train or the automobile.

In 1849 Berthold, of Göttingen, experimented by removing the testes from cocks and grafting them into another part of the body, his object being to show that they secreted a substance which, when absorbed by the blood, produced the male characters. According to Biedl, to this physiologist belongs the credit of first proving the existence of an "internal secretion." Claude Bernard believed that the glands of the body secreted both an external secretion and an internal secretion, the latter being delivered straight into the blood. Brown-Séquard is generally admitted to be the founder of the practice of organo-therapy, for he was the first to demonstrate the value of administering extracts of glands.

The chemical agents which excite the functions of other organs have been termed hormones; in fact, this term has largely been adopted to denote any chemical —be it excitatory or depressant—which is secreted into the blood. Schäfer has suggested that the term "autacoid" should be used generically to denote an internal secretion; the term "hormone," he thinks, should be kept for an internal secretion which excites, to distinguish it from a "chalone," or one which has an inhibitory action. As, however, the term hormone is in more or less general use to denote an internal secretion, we shall use it here in its wide meaning.

Hormones.

The substances which exert a chemical action upon the blood in its passage through an organ have been called "hormones" (*ὁρμάω* = "I excite"). The term owes its origin to Bayliss and Starling, who proposed its use for those physiological substances which act as chemical stimulants. Examples of this are to be found in the processes of digestion, where the entrance of the chyme into the small intestine causes the production of secretin, which stimulates the liver, pancreas, and intestinal glands. Again, the influence which a gland like the thyroid exerts upon other glands and their secretions is apparent: remove the gland or its secretion and the entire bodily metabolism is upset. "All organs which supply substances which are capable of exciting or in any way of affecting the functions of other organs may be described as 'hormone-producing'" (Biedl). "Material which is passed into the blood or lymph from any tissue or organ of the body forms its internal secretion, and organs which are not known to possess any other function than that of passing such material into the blood or lymph are internally secreting or endocrine organs" (Schäfer).

It is well known that not only glands without ducts (the "ductless glands"), but also glands with ducts, "epithelial elements," mucous membranes, and so on, must be included among the organs of internal secretion if they supply a hormone to the blood. Little is known, however, of the exact form in which the hormones reach the blood-stream, or the chemical means by which they modify it. Most of our knowledge has been gained by experimental physiology, and some by clinical medicine. It has been shown that removal of the thyroid profoundly affects metabolism and always in a certain definite manner; that removal of the parathyroids (in animals) leads to symptoms of nervous excitability and death; and that castration is followed by changes which vary within certain well-defined limits. Therefore, the glands in question contribute to the general metabolism some substance, the loss of which is followed by a general disturbance. Now, it is obvious that this substance is a chemical agent, for experiments by grafting have proved beyond doubt that the missing hormone can be supplied to the body if the gland is so attached that its contents can be delivered into the blood.

According to one view, only those organs which possess "differentiated epithelial cells" can justly be regarded as "internal secretory" in the strict sense of the term. But it is obvious that this interpretation of the term is too narrow, for the chromaffin tissue—the corner-stone of the endocrine system—would be excluded. From the physiological standpoint all organs, whether possessing a duct or not, which exert a specific influence on the blood circulating through them are to be regarded as organs of internal secretion.

As we noted in the case of *secretin,* where one chemical agent stimulates another, which in turn activates a third, we have a process started depending entirely upon a hormone-action. The internal secretory organs, then, are important on account of the hormones which they secrete. These are chemical substances of low molecular weight, which are not destroyed by heating, but are rendered inert by prolonged boiling. They are destroyed by oxidizing agents, and, except in the case of thyro-iodin, do not leave the body in the excretions.

The secretion of the thyroid gland, or thyro-iodin, consists of a substance rich in iodine in organic combination, which is present in the colloid of the vesicles. Removal of the thyroid produces symptoms presently to be described. The secretion of the adrenal medulla, first isolated by Takamine as ortho-dioxyphenyl-ethanol-methylamine, is present in the proportion of 1 part to 1,000 of the whole gland. Recent work on the subject of the chromaffin system has caused physiologists to regard this tissue as even more important than formerly;

and some authorities, notably Sajous, attribute to the adrenal system influences of the widest nature. References to his views on this subject will be found in Chapter VI.

Hormones fall roughly into two classes, according to their mode of origin. They may be formed by definite structures, whose sole function is the production of the product; or they may be the end products of metabolism. The secretion of the thyroid may be regarded as an example of the former class; the formation of carbon dioxide, with its specific action as a stimulant upon the respiratory centre, is a hormone belonging to the second group. The regulation of respiration is now believed to be due to chemical action. It is not regulated, but may be modified by nervous stimulation.

Our knowledge of the exact chemical nature of hormones is very small. It is known that there is a large range of action in the physiology of the body, due to their presence in the blood-stream and in some cases their specific action on the various organs; but their exact formation and action is not always known. Claude Bernard's original theory was that glandular products modified the composition of the blood; while the school that followed Brown-Séquard's ideas believe that the internal secretions have a "specific elective power," which, as Gley says, is "properly a physiological idea." "What there is characteristic about this . . . is that we are now dealing with functional actions which have neither cause, nor reason, nor an end of their own; but each one of these acts depends on another physiological action; and this dependence appears to be always of a chemical nature, be it direct or indirect, being accomplished through the intermediary action of the nervous system."*

From this standpoint we pass naturally to a consideration of the functional correlation of the various internal secretions. We can realize that the theory of inter-relationship between the various humoral influences of the body goes a long way towards influencing many physiological and some pathological facts which have, up to now, puzzled us. They can be regarded as not dissimilar to the drugs of the pharmacopœia, for they are present in the body to be utilized when the occasion arises. As we shall see in discussing the relation between the endocrine organs and the nervous system, a sudden call for increased energy is responded to by the adrenals, and to some extent by the thyroid. A less urgent message would perhaps require the co-operation of other hormones. The growth of the body requires the action and interaction of many internal secretions, the thyroid, pituitary, thymus, suprarenals, gonads, and digestive glands. Indeed, we must widen our view where such a subject as growth is concerned, and believe that almost any hormone, if missing, may disturb the development of the organs with their attached functions.

As we have already said, histological facts have to be considered when we are studying hormone-produc-

* "The Internal Secretions," by E. Gley, p. 61.

tion. Epithelium gives us a locality; its secretion introduces chemical factors; while the action of this secretion invades the realm of physiology. We cannot afford to be over-precise in discussing which hormones can justly be included among the internal secretions, and which must be barred because they fail to fulfil certain criteria. The thyroid gland, for example, is, without doubt, an organ of internal secretion; yet, as Gley points out, no specific chemical has yet been found in the venous blood of that organ. Experiments in animals and clinical evidence combine together to prove that this gland is essential to health; we must, therefore, accept this evidence as contributing a proof that this, and probably many other, hormones profoundly influence metabolism, although we are as yet unable to point to the exact means by which this is brought about. The inter-relationship between the various hormones and the manner in which one influences another, which in turn activates a third, has been proved since the work of Starling on *secretin*. The combination of many of the internal secretions, and the manner in which the removal of one upsets the endocrine balance, can best be understood by studying their inter-relationships.

The Inter-Relations of the Ductless Glands.

While the theory of the internal secretions dates back for years, and while our practical knowledge of their importance is over half a century old, it is only of recent years that we have realized how the various hormones act and inter-act to produce normal function. At the present time we know enough of the ductless glands and their inter-relation to convince us that normal health is largely dependent upon their smooth workings.

The changes in metabolism which are seen in myxœdema have their analogy in the mental sluggishness characteristic of this state, while the psychical excitability of hyperthyroidism is in keeping with the speed of the bodily metabolic changes. No part of the individual appears to escape when once a vital chemical becomes exaggerated or eclipsed; its place in the physiological dovetailing must be exact if we are to expect normal health.

The thyro-parathyroid apparatus affords us an excellent example of this, as experiments upon thyroid extirpation show very clearly the effects of thyroid deprivation upon the organism. Early experiments to determine the exact rule of the thyroid were complicated by one factor—namely, the presence of accessory thyroids—thyroid "rests," and those small glands the parathyroids. Again, experimental removal of the gland showed results which differed according to the animal operated upon. In the dog, cat, and monkey, the upper parathyroid is usually embedded in the substance of the thyroid; but, as Gley has pointed out, in the rabbit one of the parathyroids is constantly detached from the thyroid.

This factor accounts for the different results which were recorded after thyroidectomy—in some cases tetany following thyroidectomy, in others this state not supervening upon the operation. The difference depended upon whether all parathyroid tissue was removed with the thyroid, or whether some was left behind. In the former case the animal died, usually within a few days, the symptoms consisting of nervous excitability, exaggeration of the reflexes, clonic contractions of the limbs, and undue irritability to any stimuli, convulsions and sometimes diarrhœa, and vomiting.

This state is known as "tetany," and is undoubtedly due to loss of the parathyroids, the result being brought about by action on the lower neurons, for Horsley stated that it was not affected by ablation of the cerebral cortex. Even more striking in the etiology of this state is the fact that it is relieved by injections of parathyroid extract, or by the grafting of parathyroid gland into the animal. In one animal, operated on by Vassale, in whom three of the parathyroids had been removed, the animal was liable to convulsions during pregnancy, and when flesh food was given the convulsions were worse.*

The effects of removal or atrophy of the thyroid gland are, briefly, as follows: adiposity, thickening of the integument, loss of hair, loss of muscular tone,

* In some cases of exophthalmic goitre, possibly of toxic origin, many of the symptoms are relieved, certainly in some cases which the writer has had under observation, by the withdrawal of animal food.

anæmia, lowering of the bodily temperature, with sensations of chilliness, and retardation of the rate of the heart. There is an increased tolerance to carbohydrates, so that large quantities of sugar and starch have to be given before glycosuria is produced, while the mental functions become sluggish and the intellect clouded. As is well known, juvenile myxœdema or cretinism—a condition presenting most of the above features—is due to an absence or degeneration of the gland before puberty, but associated, of course, with diminished growth.

Turning to the rôle of the thyroid in health, we may summarize its functions by saying that it is one of the most important "regulators of metabolism" which the body possesses. Its action upon the circulation is that of a stimulant; its secretion is an essential chemical for the nutrition of the integument and the epidermal structures as a whole. When thyroid deficiency is present there is loss of elasticity of the skin, caries of the teeth, loss of lustre in the hair, ridged and dull nails, and frequently pruritus. The rôle of the thyroid secretion is, then, to regulate the elimination of the body, to increase the tone of the muscles, to assist in the nutrition of all the cells, particularly those of the epidermal appendages, and to prevent accumulation of waste-products, especially in the subcutaneous tissues and muscles. Hence in thyroid deprivation we find that:

1. The protein metabolism is decreased.
2. The fat metabolism is probably likewise lessened.

3. The carbohydrate metabolism is markedly retarded.

We are justified in assuming that where symptoms of retarded metabolism and sluggish circulation are present, we shall find that thyroid under-action is present. Furthermore, the chromaffin system, which is concerned in the mobilization of sugar, is affected adversely by the removal of the secretion of the thyroid; probably this may be another factor in the production of increased sugar tolerance in thyreopriva.

The results of administering extract of the thyroid are very striking, and will be considered in detail in subsequent chapters. Here we are concerned more with the physiology of the gland and its inter-relationship with other of the endocrine organs, and with the nervous system. Dealing with the first group, and taking the adrenal glands, is there a relation between these glands and the thyroid? Eppinger, Falta, and Rudinger have shown that adrenalin, which normally, when injected, causes glycosuria, no longer does so when the thyroid has been removed, but does so after extract of thyroid has been administered. But opinion is not unanimous in supporting the result which appears to indicate this inter-relationship. Gley sums up the question as follows: " (*a*) Is the thyroid secretion really an excitant of the suprarenal? and does the suprarenal blood therefore contain more adrenalin after the injection of thyroid extract? (*b*) Do extracts of suprarenal glands of thyroidectomized animals which succumbed to the operation contain less adrenalin? On these two points I have collected a large number of facts. These facts prove that the adrenals of thyroidectomized animals do not contain less active adrenalin than those of normal animals and, furthermore, that the suprarenal blood does not become richer in adrenalin after the injection of thyroid extract in physiological doses than after that of any other organic extract, at least of those which have been tested in the experiments of Gley and Quinquaud—viz., hepatic, pancreatic, testicular, and renal."*

It will be seen from this quotation that the reciprocal action of the thyroid and adrenals is not supported by Gley's work; rather would it seem that the results referred to which appear to point to this action might conceivably be due to the injection of any organic extract and not to the fact that it was thyroid extract which was utilized.

A reciprocal action between the thyroid and the pancreas has been suggested, and Lorand says that "extirpation of the thyroid suppresses glycosuria in depancreatinized animals."† Gley doubts whether this is so, and suggests that this explanation ignores many important points. Again, inter-relationship between the thyroid and the sexual organs appears to exist; certainly many suggestive signs point to this conclusion. The testis and the thyroid appear to have a relation, likewise the ovary; and it is well known

* "The Internal Secretions," by G. Gley (translated by Fischberg), pp. 206-207.

† *Ibid.*, p. 208.

that the thyroid gland tends to enlarge at the times of puberty, the catamenia, and the menopause. The ovaries exert an inhibitory action upon the thyroid, the size of the latter gland increasing after castration.

In some cases of cretinism, the anterior lobe of the pituitary has been found to be enlarged, but this is not always so. It has been suggested that this enlargement is due to a compensatory hypertrophy—a kind of "defensive balancing" of the endocrine system. The inter-relation between the thyroid and the pituitary appears to be a close one; for experimental removal of the former causes hypertrophy of the latter, and Cushing states that removal of the pituitary in young dogs causes hypertrophy of the thyroid.

The interaction of the thyroid and the thymus is less well established, although some results suggestive of such a relationship have been recorded. The thymus is usually hypertrophic in Graves' disease, and it is therefore believed to exert an antagonizing action. The thyroid and parathyroids are believed to exist in antagonistic relationship, certainly in so far as their action upon the nervous system is concerned. The parathyroids resemble the thymus in this respect, for their removal is followed by nervous symptoms. Paton suggests that both exert "a depressing or regulating effect upon the spinal synapses, an action opposite to that of the thyroid."

There is a definite antagonism between the pancreatic secretion and the chromaffin, certainly in so far as the mobilization of sugar is concerned. The internal secretion of the pancreas checks the mobilizing of sugar, while adrenalin hastens it. It is believed that adrenalin acts by stimulating the sympathetic endings in the liver; perhaps, as Paton suggests, "the endocrinous secretion of the pancreas inhibits them." The interaction of the pancreas and the thyroid is indicated by the occurrence of glycosuria in Graves' disease and by the experiment of Lorand, which showed that removal of the thyroid in a dog suffering from pancreatic diabetes reduced the glycosuria; also by the observation of Eppinger, Falta, and Rudinger, already referred to, that after thyroidectomy adrenalin produces glycosuria less readily.

There is a reciprocal action between the gonads and the thyroid, for thyroidectomy stops the growth of the sexual glands, although castration does not have a similar effect upon the thyroid. Both the thyroid and the gonads, moreover, have a stimulating, although not an exactly similar, effect upon growth. The testes are helped in this relation by the thymus, for this gland appears to check the growth of the testes, while the latter exert a similar action on the thymus.

The relation between the gonads and the pituitary is interesting. Destroying the pituitary causes atrophy of the gonads, but castration causes hypertrophy of the former gland; the pituitary therefore has a stimulating action on the gonads, but these have an inhibitory action on the pituitary (Paton). Both exert a stimulating action on growth, while the pituitary, when unchecked by the controlling action of the gonads, produces gigantism and acromegaly.

There is a suggested relationship between the sex organs and the parathyroids, which is seen in the observation that pregnancy increases the symptoms of hypo-parathyroidism. Little is known, however, of this inter-relation.

Interesting observations as to the relationship between the adrenals and the sexual organs have been made. It is believed that this relation is a particularly close one; indeed, Sajous suggests that the testicle does not produce an internal secretion, but that the adrenal rests which are contained in this organ are responsible for the "elaboration of the sperm." Several instances are on record in which precocious development and early appearance of the secondary sexual characteristics have been associated with a tumour of the adrenal body; moreover, on the removal of the tumour these signs have subsided.* Further, the symptoms and signs of testicular tumour (from the cells of Leydig) are precisely those seen in a growth of the adrenal cortex. Tumours in the latter situation occur usually in children and are associated with premature development, so that a child of seven or ten years may have the characteristics of an adult woman; marked growth of hair on the head and body, and a tendency to male characteristics, such as a deep voice, and over-development of the clitoris. Sajous

* Quoted by Sajous, "Internal Secretions and Principles of Medicines," pp. 474-476.

concludes, therefore, that "it is to the secretion of the adrenal tissues, wherever situated, that the male characteristics are due."*

It is interesting to compare the above description of the signs of adrenal over-activity with those typical of hypo-adrenia—namely, muscular weakness, loss of flesh, feeble cardiac action, low blood-pressure, constipation, deficient growth of hair, pallor, and mental sluggishness. These symptoms, of course, when due to disease of the suprarenal bodies, constitute the disorder known as Addison's disease.

The ovary possesses analogous properties—from the point of view of the internal secretions—to the testis, up to a certain point, but then the analogy ceases. Removal of the ovaries in the young female produces results similar to those seen after castration in the young male—namely, an infantile type of the genital organs and a non-development of the mammæ; while after ovariectomy in the adult there is a retrogressive change seen in the uterus and mammæ, and a cessation of menstruation. Again, the influence on metabolism of the ovarian secretion is analogous to that of the testis—in other words, it increases oxidation and metabolism, so that its removal produces obesity and a sluggish circulation.

It is claimed by many authorities that administration of ovarian extract increases oxidation, particularly of phosphorus products, hydrocarbons, and fats. The clinical reports of the results following ovarian organo-

* *Ibid.*, p. 477.

therapy are striking, and there can be little doubt that this substance possesses a real value in enhancing the deficient metabolism consequent upon ovarian atrophy.

The question "To what part of the ovary is this action due?" is not so easy to answer. The three possibilities are the interstitial cells, the Graafian follicles, and the corpora lutea. The latter possess, it is said, all the properties which characterize the chromaffin tissue, and, furthermore, show the signs suggestive of an internal secretory organ, being extremely vascular, and related in development intimately with the mammary gland, destruction of the corpus luteum arresting the development of the mammæ.

The interstitial gland, on the other hand, behaves in many ways, as do the corpora lutea. It attains to greatest development during pregnancy and becomes enlarged during menstruation. This body is believed to possess many of the characteristics of adrenal tissue. "We know that, in addition to the Graafian follicles, the ovary contains two other tissues, both of which, from the nature of their structure, might possess an internal secretory function, but which in their origin differ fundamentally from one another. These are the corpus luteum, which is derived from the epithelium, and the interstitial stroma cells, which have a connective-tissue origin. That the interstitial stroma cells possess a secretory function is suggested by the presence of fat granules and other secretory enclosures, as well as a certain resemblance, commented upon by many (Mulon, Wallart), to the cells of the suprarenal cortex."*

After discussing the theories which connect ovulation and menstruation, Biedl says: "Hence we are forced to assume a continuous production of the hormone by which these changes are effected, the source of which can only be either in the Graafian follicle itself or in the interstitial tissue. But the Graafian follicles are already present in the immature ovary, and for that reason they can hardly be credited with the same significance in this connection as the interstitial gland, which attains its full development at puberty, shows signs of a cyclic increase of function corresponding with menstruation, and which, at the climacteric, undergoes involution."†

Sajous believes that the secondary sex characteristics in the female owe their origin to the interstitial cells, which "correspond morphologically and chemically with those of the adrenal cortex." The analogy is clear, but he states definitely that these cells are not the same structure as the cells of Leydig in the male; and he adds that "there is no true internal secretion of the ovaries, the products of the Graafian follicles and their corpora lutea and of the interstitial stroma cells being derived mainly from adrenal rests in those cells."

We have discussed the inter-relationship of the ductless glands, and shown that removal of one secre-

* "The Internal Secretory Organs," p. 401.

† *Ibid.*, p. 403.

tion produces effects which, in many instances, arise as the result of the absence of the secretion and its "balancing power." We must now consider the question, "How is this relationship governed?"

It is at once obvious that the controlling factor may be chemical or it may be nervous. In other words, the internal secretions may produce their own control by chemical balancing, or the helm may be controlled from the central nervous system. The effect of a graft upon the body is strongly suggestive that the chemical action is the prominent factor; for it matters not in what part of the body the graft is implanted, so long as the secretion arising in the gland finds its way into the blood-stream, the effects of the extirpation of the gland are abolished or delayed. This would scarcely be so if nervous stimuli were essential to the production of a particular hormone. On the other hand, it would be foolish to assume that the inter-relationships were purely chemical and entirely free from the supervision of the nervous system.

Turning for a moment to the digestive system, we know that the stimulus which excites salivary secretion is often nervous, and that gastric secretion depends, at all events for its commencement, upon the same stimulant. Subsequent digestion, it is true, is carried on largely by chemical messages. Again, the production of adrenalin is under the control of the nervous system, although its function is assisted, correlated, and sometimes neutralized, by chemical agents.

The answer to our question is, on the face of it, exceedingly difficult, and, moreover, is complicated by the fact that removal of an organ is not invariably followed by the same result. We have already seen that in some cases of hypothyroidism the anterior lobe of the pituitary is enlarged, but this is not always so. It is possible, as Paton suggests, that the enlargement, when present, is a defensive one, and that its absence makes the condition of the individual worse. The part played by the nervous system in the control of the endocrinous glands can, however, scarcely be overlooked, or even despised, in view of the results of recent research. We know that intense pain produces an increased flow of adrenalin, and that its pathway is viâ the sympathetic system. Emotional activity, if sufficiently intense, is followed by a similar result. The similarity between the chromaffin system and the sympathetic is exceedingly close, and the former is the keystone of the endocrine system.*

It would seem, therefore, that there is an interaction of a chemical nature, which functions as a control; and the evidence serves to show that control is exercised, certainly in some instances, by the nervous system. With the facts at our disposal we cannot answer the question more certainly, but must await the establishing of fresh evidence.

* This subject is discussed at greater length in Chapter XI.

CHAPTER II

THE THYROID AND PARATHYROID GLANDS

In the Introduction we briefly reviewed the present place of the endocrine glands in medicine, and suggested some practical points in connection with hormone-therapy. We now propose to discuss in a little more detail the more important of the ductless glands, laying emphasis upon the known results of administration of the extract of these glands, and the signs pointing to deficiency or excess of secretion.

Naturally, the thyroid gland first deserves our attention, and for several reasons. More is known of its characteristics, secretion, functions, and disorders; it takes a particularly important place in medicine on account of the frequency with which disorders of its functions are encountered; and, finally, of all the ductless glands whose secretions have been utilized in the form of extracts for oral or hypodermic injections, the thyroid gland has given the best and most astonishing results. From the moment when G. R. Murray first published the results achieved by administering thyroid extract to a patient suffering from myxœdema (October 10, 1891), great interest has been aroused in the practice of organo-therapy, an interest which Brown-Séquard's previous statements on the results of feeding with testicular extract had failed to arouse.

In 1890, Vassale in Italy and Gley in France experimented with injections of thyroid extract to animals who had been deprived of their thyroids, and demonstrated that these animals could be kept alive by such injections. This was followed shortly afterwards by the application of this discovery to therapeutics, when Murray treated his case of myxœdema by thyroid extracts and established that this condition could be cured by these means. Previous to this date, Gull and Ord in England had investigated myxœdema, and Kocher had described a condition following the removal of the thyroid, which, from the similarity of its symptom-complex, was shown to be identical with the spontaneous condition already named myxœdema.

As far back as 1859, Schiff discovered the fatal result which accrued from the total removal of this gland, and later, when Kocher described "cachexia strumipriva," or the condition of post-operative myxœdema which followed so many of his early operations for goitre, this fact attracted wide attention. Schiff and subsequent observers also discovered that transplanting the gland beneath the skin relieved the symptoms. Unfortunately, it has now been shown that an implanted gland is very liable to absorption, and thus to lose its utility.

These researches had established the fact that removal of the thyroid gland was followed by a train of symptoms which constituted the condition named "myxœdema."* A fresh factor then arose, on account of the discovery of two pairs of small glands, situated on either side of, and deep to, the lateral lobes of the thyroid, which received the name of "parathyroids." It was maintained by some authorities that the symptoms which followed the removal of the thyroid gland were due to the removal of these small glands, and in support of this theory it was adduced that, while removal of the thyroid alone was not usually fatal, removal of both thyroid and parathyroids proved rapidly fatal. On the other hand, some observers maintained that it was impossible to remove the parathyroids without alto interfering with the integrity of the thyroid. Forsyth concludes, from the result of his investigations, that the parathyroids have no connection with tetany, and in this he is in opposition to most observers. We shall have more to say about this when we are dealing with the functions of the parathyroids.

Histology and Physiology of the Thyroid Gland.

The thyroid gland is developed by a median outgrowth from the entoderm lining the pharynx between the first and second branchial pouches. A solid mass of cells bifurcates at the upper end of the trachea: the

* This name came into existence on account of the believed existence of excess of mucin in the subcutaneous tissues in these cases.

median portion becomes the thyro-glossal duct, which afterwards becomes obliterated; the lateral portions divide into many branches and form hollow tubes, which become closed vesicles. The thyro-glossal duct, through which the secretion was originally discharged, becomes obliterated, the foramen cæcum at the base of the tongue remaining to mark the site. Langdon Brown suggests that thyroid extract is absorbed unaltered from the alimentary tract because the duct originally carries the thyroid secretion there.

The thyroid gland, therefore, belongs to the group of ductless glands—that is to say, its secretion is poured into the blood-stream direct, and not by means of a duct. It is situated in the neck, and consists of two lobes, one on each side of the trachea, extending upwards to the thyroid cartilage, covering its inferior cornu and part of its body. Joining these two lobes is the isthmus. The gland is surrounded by a capsule, and is composed of vesicles lined with cylindrical or cubical cells. These vesicles contain the typical colloid material, iodothyrin, which is composed of iodine in combination with an active principle which has the characters of a globulin. Its recognition we owe to Buamann of Freiburg, who discovered its existence in 1896. Herbivora possess it in abundance, as most vegetables contain iodine. The weight of the gland varies between 32 and 60 grammes; it is larger in females than in males, and undergoes changes in size at the menstrual periods, and at such times as puberty and the climacteric; it is liable to swell under marked excitement and during emotional strain.

The colloid with which the vesicles are filled plays an important part in general bodily metabolism. In man there is nearly always sufficient for it to be discovered analytically (in normal health), but Wells states that the actual amount varies with the locality. It is scanty in young children and in parenchymatous goitre; unusually high in exophthalmic goitre. It has been suggested that an important function of the thyroid gland is to control the iodine metabolism of the body.

Now what are the results of removal of the gland in man? When we come to review the knowledge which experimental physiology has given us, we are at first rather bewildered by the apparent contradiction which faces us. Early observations upon the effects which followed the removal of the gland in animals showed that in carnivora the effects were very severe, and often fatal, tetany supervening and the animal dying from cachexia. In herbivora, however, the results of such an operation were often exceedingly slight, and were confined to a slight cachexia, but sometimes a rapidly fatal result ensued. The first inference to be drawn from this was that a meat diet was the important factor which accounted for the difference between the effects in carnivorous and herbivorous animals. Gley, however, showed that the explanation was quite different, and he proved that the parathyroids (one pair, now usually known as the "external parathyroids") were responsible for the wide difference in the results. He demonstrated that these small glands were so situated in carnivora that, when the thyroid was removed, the parathyroids were also removed; whereas in herbivora they were as habitually left behind. When the operations were made identical the results were approximated.

This originated the view now widely held, which regards the nervous symptoms following removal as attributable to the loss of the parathyroids—the effects of thyroid removal alone being, in the young a condition analogous to cretinism, in the adult a cachectic condition. Indeed, in the young animal the effects of thyroid extirpation are much more marked than in the adult animal. A few of the changes produced are striking. As we have already said, a cretinoid condition results, with delayed ossification of epiphyses, diminished development of the bones of the skull, protuberant abdomen, relaxation of the ligaments of the spinal column, and sexual infantilism. Alterations in the growth of the hair are observed in some species, and, most interesting of all, an extensive atheromatous degeneration of the aorta is found, which bears out the hypothesis that the function of this gland is concerned with calcium metabolism. Previous to this discovery Horsley had surmised that many of the features of thyroid inadequacy resembled those which characterize senile decay.

Where thyroid secretion is excessive, we know that there is increased calcium leaving the body; and, in those patients exhibiting deficiency of thyroid, we may assume that increase of the calcium salts at the disposal of the metabolism results in an atheroma—a laying down of this substance in the walls of the arteries.

After thyroid extirpation there are several changes which deserve special mention. There is a marked retardation in metabolism in general, nitrogenous metabolism is greatly reduced, fat metabolism is likewise diminished, as the tendency to the deposition of fat in myxœdema shows. The animal without a thyroid exhibits excessive tolerance to carbohydrates; it can take abnormally large amounts without suffering from glycosuria. The reduction in the metabolic exchanges naturally diminishes heat production, and this point is of interest from the practical standpoint, human beings with deficient thyroid secretion being more susceptible to cold, and suffering increased discomfort in the winter months. As opposed to this, patients with Graves' disease rarely suffer any inconvenience from cold, but feel the heat of the summer months to be almost insupportable. As is well known, they are nervous and restless, and the increased tissue wastage produces a rapid loss of flesh, and in some cases actual emaciation.

The Parathyroid Glands.

Turning now to the parathyroids, whose existence, it will be remembered, is of more recent discovery, we find that there are two pairs of these glands, situated, as we have already said, in close proximity to the lateral lobes of the thyroid gland itself. In structure they bear some resemblance to this latter gland, resembling it, however, more in its embryonic characteristics. They are formed of columns of granular epithelium cells, and show a very vascular connective tissue between these. It has been stated that, if these glands are left when the thyroid has been removed, they undergo a marked hypertrophy.

To Sandström belongs the credit of first accurately describing these little glands. His view was that they were in reality embryonic rests of thyroid tissue proper. At the present time, although our knowledge of their functions has advanced somewhat, much of the knowledge we possess may be described as more speculative than proven.

The parathyroids are formed as epithelial outgrowths from the third and fourth branchial clefts; the lower parathyroid (parathyroid III.) lies sometimes in contact with the lower pole of the thyroid, or sometimes farther away, as low down as the thymus (Schäfer), while the upper parathyroid (parathyroid IV.) is usually in contact with the upper border of the thyroid near the dorsal aspect. From the fact that, in many animals, the upper parathyroid is embedded in the substance of the thyroid, the name "internal" parathyroid has been given to it, the lower parathyroid being known as the "external" parathyroid.

MacCullum came to the conclusion that they controlled in some way the calcium metabolism of the body. Calcium moderates the activity of nerve cells;

therefore, when the secretion of the parathyroids is deficient, and calcium is lost from the nerve cells, the patient will suffer from an exaggeration of nervous excitability. This corresponds to the surmises as to the causation of the nervous symptoms which are manifest when the thyroid has been extirpated. In support of this view, the administration of extracts of the parathyroid glands in cases of tetany has been proved to be efficacious in controlling the convulsions. It will be remembered that tetany is a prominent symptom after extirpation operations in animals. Likewise the administration of calcium salts will control the symptoms of tetany.

Opposed to the views just quoted, some observers believe that the parathyroids are portions of the true thyroid gland; that they have become separated from the gland itself, or that they secrete the same colloid, although they have not as yet formed vesicles; or that they develop into normal thyroid tissue, intermediate types having been noticed.

It is stated that if all four parathyroids are removed the animal succumbs rapidly, no matter whether the thyroid is left intact or not. If one parathyroid be left, death does not usually ensue, although tetany may be brought on. It has also been said that changes in these glands are very common in cases of tetany in children, in pregnant women, and in osteomalacia (a disease associated with defective calcium metabolism). This would seem to be supported by the beneficial effects of calcium administered by the mouth, as it would tend to replace the excessive loss of calcium due to the defective parathyroid secretion.

With the few facts at our disposal, and the many speculative theories based thereon, it is natural that many diseases should have been attributed to an abnormality of these glands. To take one example, it has been suggested that paralysis agitans may be due to disease of the parathyroid glands, but, unfortunately, it does not appear to benefit by the exhibition of extracts of these glands.* This is, of course, not tantamount to a refutation of this theory, as it may mean that the extract undergoes changes during its passage through the body which rob it of its natural properties, so that it is unable to replace the normal secretion which should be delivered into the blood-stream. The only instance which, so far as I am aware, has been published in which parathyroid extract appears to have been absolutely successful, and to have been, if one may use the expression, specific, is described by Hurst in the *Practitioner* for January, 1915, in an article on the parathyroids. Briefly, this case was a man of middle age, who had suffered from an enlargement of the thyroid gland, and had undergone an operation in which the greater part of it was removed. He remained well for two years, and then suddenly became

* An interesting case of paralysis agitans, in which progressive atrophy of the globus pallidus was found, is described in the *Medical Annual*, 1918, p. 404.

very restless, tremulous, and developed fibrillary tremors and other signs which closely resembled Graves' disease. His hair ceased to grow, he became impotent, his bowels were loose, and his weight decreased very rapidly.

No treatment was of much avail, and the administration of dry thyroid gland aggravated the symptoms. He was given dry ox parathyroid by the mouth, and from that day he began to improve, became stronger, increased very markedly in weight, and returned to work. Not until he had been taking the parathyroid gland for six months did his sexual powers return. Hurst thus concludes the account of this very interesting case: "His weight in February, 1914, had risen to 189 pounds; he felt perfectly well and strong, and no trace of nervousness remained, although he was working very hard."

Here, apparently, was a case in which the secretion of the parathyroids was deficient, and where its administration by the mouth was able to replace the normal secretion.

If this latter surmise be correct, it would seem that it is possible for an analogous treatment to that of myxœdema to be initiated, if only we could arrive at an accurate diagnosis. It would support the school which believes in the separate functioning of the thyroid and parathyroid, and might eventually show us where we are lacking in the treatment of exophthalmic goitre. It is certain that the removal of part of the thyroid does not cure this disease, although it may ameliorate the symptoms for a variable time. If the nervous symptoms are due to excess of thyroid secretion, then removal of part of the gland should counteract the excess. But if this group of the many symptoms of Graves' disease owes its existence to an abnormality of the parathyroids, we must alter our surgical treatment of this disease.

On the other hand, we have yet to study the views of that school which has returned to Gley's original belief: that the parathyroids are part of the thyroid gland; that they are an embryonic and partly developed thyroid tissue. In support of this view, it is stated that post-operative tetany is greatly benefited by administering thyroid gland by the mouth, and that pure parathyroid, even in larger amounts, has not given the same results. It would appear from this that tetany owes its origin to deficient thyroid, and not necessarily deficient parathyroid, although the ordinary sheep's thyroid gland contains parathyroid substance.

This school, therefore, regards the parathyroids as part of the thyroid, and not separate structures; their function would be similar, and it follows from this hypothesis that the diseases which have been tentatively attributed to the parathyroids (mainly on account of the similarity which their symptom-complexes bear to those produced experimentally) must in reality owe their origin to the thyroid—assuming that they are in any way connected with this gland. This is comforting, as it narrows the field of inquiry: it leaves us one set of riddles to solve instead of two. But we must admit that this view is not widely accepted, mainly on account of the many small facts which have been collecting, albeit slowly, to show us that the parathyroids are undeserving of neglect.

Functions of the Thyroid Gland.

We must now leave the subject of the parathyroid glands, and, before concluding this chapter, briefly review the theories which endeavour to account for the work of the normal thyroid gland. What is the function of the thyroid? Does it govern metabolism? Is it a "vital antiseptic"? Or is it concerned with growth alone? The only way in which we can attempt an answer to these questions is to give some few facts and more theories dealing with the function of this gland.

Firstly, then, the thyroid gland possesses the peculiar property—peculiar in the sense that it is not shared, so far as we know, by the other endocrinic glands—of being able to store its secretion. This is proven by the fact that, in cases where the gland has atrophied or been removed, its secretion can be replaced by artificial ingestion. We quite naturally turn to the colloid as being the stored-up secretion, and, indeed, we are justified in so doing, as there is evidence to show that this substance arises as droplets in the epithelial cells lining the vesicles (Dale). Again, this secretion contains a relatively large percentage of iodine (0·2 per cent.), and on this fact, or partly on this fact, has arisen the theory that the thyroid has a phagocytic or antitoxic action. In young animals, however, the iodine-content is very small, and in adult animals it appears to bear a direct ratio to the iodine-content of the food. On the other hand, there is no reason to suppose that the power of the body to resist intoxication is raised when iodine or the iodides are given by the mouth; although Hunt found that young thyroids had some power to raise the resistance to a particular substance (acetonitrile), and that this power ran more or less roughly parallel to the iodine-content.

In this connection, the action of iodides upon gummata is of interest; and, as pointed out by Rendle Short, the beneficial action of these drugs is in reality due to the increased action of the thyroid which is engendered by the administration. He says: "I have found thyroid extract quite as effectual as iodide of potassium in healing tertiary syphilitic ulcers." In speaking of the action of iodides on gummata and atheroma, he says: "In cases of myxœdema arterio-sclerosis is early and intense. The same is true in animals after removal of the thyroid."[1] Eiselsberg gives a number of very convincing photographs of intense atheroma of the aorta in his cretin lambs in which the thyroid had been removed in early life. In the second place, thyroid extract has a wonderful power over young connective tissue, as is seen by the way in which it absorbs the subcutaneous thickening of myxœdema and cretinism. It is not surprising, therefore, that it should be able to deal also with gummata and atheroma.

The theory of toxin-neutralization states that the secretion of the thyroid has the power to neutralize toxins which find their way into the blood-stream. It goes on to maintain that these toxins (of albuminoid nature) are absorbed from the alimentary canal, and undergo iodization in the thyroid by means of its secretion. It will be remembered that Lane maintains that atrophy of the thyroid gland is one of the features of chronic intestinal stasis. Is this the result of overwork? Hardly, for overwork produces hypertrophy, not atrophy; and yet, if the symptoms and signs attributed to intestinal stasis owe their origin to toxæmia, and the thyroid is the neutralizer, then (to reconcile the two theories) the thyroid should be enlarged, *not* atrophied. In other words, it should be overworked, not idle.

On the other hand, it is possible that after long-continued toxæmia the secretion of the thyroid might be used up, the reservoir, to which we have already likened the thyroid, becoming dry. That this may be so is supported by the clinical evidence in certain cases where the administration of thyroid extract, in cases of intestinal stasis, materially improves the symptoms. What has been called "the vital antiseptic" power of the thyroid may show itself in protecting the body from the toxins arising in the portal area. It has been shown, experimentally, that after ligature of the bile-ducts the thyroid colloid increases, and there is evidence to show that the itching of jaundice can be ameliorated by thyroid extract. The bile-salts in the urine gradually diminished under this treatment, and when the treatment was stopped they again appeared, to disappear as soon as thyroid was again administered.

This evidence is of great importance to the organo-therapeutist, for it suggests yet another way in which extract of thyroid can be utilized. One of the most difficult problems which confronts the clinician to-day is the diagnosis and treatment of intestinal stasis. This subject is referred to in Chapter XIV., where it is shown that thyroid extract assists in defending the body from toxæmia, especially that in which the liver is concerned.

We know, however, several facts of importance about the thyroid to balance this tangle of theories. Firstly, we know that a train of symptoms follows its deficiency or absence, whether produced experimentally or arising spontaneously, and that these symptoms will yield to thyroid feeding. The results of an extirpation operation in young animals differ only slightly from the condition which we know as cretinism, while the adult analogy of this we encounter as myxœdema.

Thyroid is therefore concerned with the growth of bone, with the development of the body, and with a normal circulation. It has been suggested that the reason why the colloid is scanty in the young is that it is used as rapidly as it can be manufactured by the gland. As we shall see when discussing thyroid deficiency, the clinical pictures of the slighter forms of inadequacy require discrimination to discover, and are as yet not sufficiently definite for their wide acceptance. But the above facts lend themselves to further investigation.

Again, in the adult, there can now be little doubt that absence or diminution of the secretion produces, or helps to produce, a condition of secondary anæmia. Whether this argues any direct connection with the hæmatopoietic system, we are unable at present to say. That the thyroid is a direct circulatory stimulant there can be little doubt; for the slow pulse, cold extremities, sluggish circulation, and deficient action of the sweat glands in submyxœdema, are very well recognized.

The interaction of the thyroid with the other ductless glands is discussed in the previous chapter, and its relation to growth and metabolism has already been referred to.

We must here leave the discussion of the thyroid and its small neighbours, realizing only too well that many blanks still remain to be filled up, which further light on this most difficult subject can alone do.*

REFERENCE.

[1] The Newer Physiology in Surgical and General Practice, by A. Rendle Short, third edition, pp. 82, 83.

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* For a fuller account of the thyroid gland, the reader is referred to McCarrison's work (see Bibliography on p. 341).

CHAPTER III

EXOPHTHALMIC GOITRE

Synonyms: Graves' Disease; Basedow's Disease; Hyperthyroidism.

WITH increasing knowledge, the conception of this disease has become a much more difficult matter than when it was regarded as being solely due to an over-action of the thyroid gland. Modern views as to the pathology of Graves' disease would have us believe that, although derangement of this gland is present in this malady, the thyroid is not the sole organ at fault, neither is a hypersecretion of this gland alone responsible for the symptoms.

Definition.

Let us for a moment refer to some definitions of this condition which have been current, and then compare these with modern views as to the etiology and pathology. In one textbook of medicine we meet the following definition: "A disease characterized by enlargement of the thyroid, exophthalmos, increased action of the heart, tremor, and nervous instability."[1] Again: "The four classical symptoms of Graves' disease are—A staring appearance of the eyes, generally spoken of as exophthalmos, though there need be no actual protrusion of the eyeballs; moderate and almost symmetrical enlargement of the thyroid gland; a pulse-rate between 120 and 180 per minute—usually about 140 when the attack is moderately severe; and extreme nervousness, with fine tremor of the outstretched fingers. When all these symptoms are present at the same time, there can be little doubt as to the diagnosis, but very often some of them are absent, and it is possible for tachycardia to be the only symptom of the disease."[2] "There are three prominent symptoms: Protrusion of the eyeballs, enlargement of the thyroid gland, and frequent action of the heart."[3] "We are accustomed to recognize three cardinal symptoms in this disease—namely, (1) tachycardia, (2) goitre, and (3) exophthalmos; but we must remember that these are not the only symptoms."[4]

These definitions represent the general views which have been held on the nature of the disease and on the most constant symptoms.

The condition was first recognized by the celebrated Dublin physician whose name it now bears about the year 1835, although Von Basedow in 1840 published a paper on the subject. Consequently the disease is in Germany and some other parts of the Continent still referred to as "Basedowsche Krankheit," or "Von Basedow's disease." However, as early as 1825 Caleb Parry, of Bath, drew attention to the condition, and, according to Osler, to him belongs the credit of first describing the disease. Many of the early conceptions of the malady have, in the fulness of time, given place to views which have been promulgated from the results of the extensive practical physiological research which has been undertaken in order to establish the causation of the disease. But it was recognized then, and it is believed now, that emotional strain can precipitate the disease. Thus, Trousseau refers to a lady who was suffering great grief at the death of her father, and had been crying for a long time; she "suddenly felt her eyes swell and lift up her eyelids." This was accompanied by copious epistaxis, violent palpitation, and throbbing and enlargement of the thyroid. A few days later the nature of the disease was recognized. Again, Stokes describes the case of a man who developed the disease from long-continued bleeding from piles; and many other records show that the etiology of the disease was universally regarded as a wide one.

From the early thirties of the last century the nature of the condition was recognized, but it is only comparatively recently that the diagnosis has been narrowed. Thus, it will be seen, from the definitions quoted above, that it is not necessary, as used to be thought, for all the classical symptoms to be present in any given case. Nevertheless, there is one symptom without which, as Mackenzie rightly insists, the condition cannot be diagnosed, and that is persistent tachycardia.

So we come down to this: that exophthalmic goitre may, and in the opinion of many observers does, exist without the exophthalmic symptom. It is, therefore, somewhat unfortunate that the name of the disease should be inseparably connected with a symptom which is by no means constant. But we cannot at the moment, at any rate, suggest any other name which is free from objection. As we shall see later the modern nomenclature which is sometimes used—namely, "hyperthyroidism"—is open to an equally serious objection, as it implies that it is always an over-action of the thyroid alone which is responsible for the features of the disease, of which we must reckon proptosis, when present, as one. Again, it has been pointed out by one observer that this latter symptom is significant of over-action, not of the thyroid, but of the adrenals.[5] Therefore, hyperthyroidism is a no more suitable label for the disease than is exophthalmic goitre. Although there seems to be an objection to utilizing the name of the discoverer of a disease to designate that disease,* in the present

* It may be affirmed that this mode of naming a disease after its discoverer is to be deprecated, partly on account of the difference of opinion as to whom the credit of the discovery really belongs, and partly because it is, perhaps, an unfortunate reward for the happy pioneer in the particular disease. Again, if a disease is discovered more or less synchronously by different observers in different countries, a nomenclature is adopted which varies with the different countries, and this all leads to confusion. If a disease is called by its most distinctive feature, this will probably be similar in different languages, so where such a course is possible it is certainly to be preferred.

instance it would seem, for the moment at any rate, to be the most satisfactory way to designate this malady. "Graves' disease" has the merit of being non-committal as to symptoms, and less unwieldy than many of the other names by which the disease has been known.

In the majority of textbooks, the malady under discussion is referred to as "exophthalmic goitre," in contradistinction to ordinary goitre. When the swelling in the neck, if present, is accompanied by the other well-recognized signs of Graves' disease, such as persistent tachycardia, exophthalmos, tremor, and other symptoms and signs to be described anon, then we diagnose the presence of this disease as opposed to simple goitre.

Etiology and Symptoms.

Graves' disease (as we shall call the malady in this book) is seen more commonly in the female sex than in the male, and more commonly in young people than in elderly. It has been seen, however, in an infant only two and a half years of age, and several cases are on record of the disease occurring in children of both sexes. Von Graefe stated that the proportion of females to males was 6 to 1, while Eulenburg said that the ratio was at least 2 to 1. Trousseau's cases show a ratio of 50 to 8, Henoch's 23 to 4, and Präel's 28 to 1. Whatever figures we study there is plainly a vast preponderance of females over males. The commonest time for the disease to develop is in the decades twenty to forty, and its features are often made manifest at critical times in the history of the patient, such as puberty, the catamenia, and the menopause. Indeed, it is said that in normal persons of the female sex the thyroid is liable to swell and to exhibit increased vascularity at these times and during sexual excitement.

As we have already indicated, there can be little doubt that, certainly in individuals prone to the disease (by this I mean persons who exhibit signs indicative of thyroid instability), a mental strain or a sudden anxiety seems to be capable of precipitating the disease. Again, there is a sufficiency of evidence to show that a parenchymatous goitre can develop into an exophthalmic goitre, given suitable opportunities. The symptom-complex which is produced by thyroid feeding on a large scale differs in many details from the symptom-complex of this disease, so, as Biedl says, we must regard the similarity of the two pictures, not as conclusive evidence that the thyroid is the organ responsible for the disease, but as very strong presumptive evidence.

The evidence includes many signs suggestive of the involvement of the adrenal system in Graves' disease, and some of the symptoms are readily explicable if we believe that the adrenal system and the thyroid are together responsible for the disease. Sajous divides the disorder into these stages: the first, or sthenic stage, "Exophthalmic goitre is due to over-activity of the thyroid and adrenal glands, and to the exaggerated tissue oxidation this entails"; the second, or asthenic stage, due to "exhaustion and functional insufficiency of the thyroid and adrenal glands, as a result of their prolonged over-activity during the sthenic stage." The disease when fully developed he describes as follows: "Exophthalmic goitre is a constitutional disease due to excessive functional activity of the thyro-parathyroid apparatus, and to the resulting dilatation of all arteries which the excess of thyro-parathyroid secretion causes by producing excessive phosphorus oxidation (and elimination as P_2O_5) in all tissues, including the vascular muscles and the depressor nerve."*

There is, according to this author and Chittenden, whom he quotes, increased phosphoric acid metabolism and excretion in this disorder, and, the brain and nervous system being especially rich in this substance, its loss is shown by nervous symptoms—agitation, restlessness, and capriciousness. This disease is, as is well known, characterized by the peculiar mental attitude possessed by the patient, to which we shall refer later. Some authors, indeed, consider that Graves' disease is, in essentials, a neurosis; and Stoddart, in comparing the symptoms of anxiety neurosis and exophthalmic goitre, says: "The two conditions differ only by one symptom or at the most two. It is therefore obvious that they are very closely allied.

* "Internal Secretions and Principles of Medicine," p. 214 *et seq.*

Although we are forced by such considerations (and others to be considered later) to the conclusion that exophthalmic goitre is a special variety of the anxiety neurosis, it would be incorrect to regard them as identical; the above remarks are merely intended to justify the classification of exophthalmic goitre as a neurosis."*

Nobody who has seen Graves' disease often will doubt the striking mental changes which occur; whether the majority of observers will agree to its classification as a neurosis is questionable. The nervous symptoms, which include muscular spasms, choreic movements, and even convulsions, are explained by Sajous as being due to "undue erethism in the cerebro-spinal axis and the peripheral nerves, and explain the excessive excretion of P_2O_5." There is, in fact, an increased wear and tear on the entire system, so that those patients lose weight, the temperature is usually raised, and in some cases a considerable rise of temperature is noted. Sajous attributes the exophthalmos to vaso-dilation of depressor origin; Stellwag's sign to the same cause. Tachycardia is partly explained as the concomitant of the febrile state, and partly as the erethism of the central nervous system and the nerves themselves, including the accelerator nerve.

The facts and their explanations here quoted certainly offer an easily acceptable guide to the underlying pathology of Graves' disease. The summary of these conclusions is that exophthalmic goitre can be divided

* "Mind and its Disorders," third edition, p. 223.

into stages, according to the degree of over-action of the thyroid and adrenal systems; that one or other of these organs is at a given stage in the ascendant, and according to which it is, so will the signs, particularly those referable to the circulatory system, vary. The two stages above referred to may lead to a third—namely, "asthenic or myxœdematous state"—in which there is exhaustion of both the thyroid and the adrenals.

When we come to study the symptoms of Graves' disease, we see three or four definite and fairly constant features, and a multitude of smaller and somewhat vaguer signs. There can be little doubt that tachycardia deserves the first mention, as it is very constant, and may be looked upon as a fundamental sign of this disease. Indeed, it is one of the symptoms which can always be produced by the ingestion of thyroid extract; and there must be very few cases of undoubted exophthalmic goitre which do not show this sign. The pulse is usually rapid, ranging from 100 to 140 or more per minute. The pulse-wave is not always thin; indeed, in many cases a full and bounding pulse is observed. Again, it is usually regular, but the rate increases upon very slight exertion.

In this connection it is interesting to refer to the theory which Eppinger and Hess brought forward. They consider that the symptoms seen in Graves' disease enable us to divide these cases into two groups. In the first the symptoms of sympathetic excitement predominate, and these they describe as sympathetico-tonic; while the second group is described as vagotonic, from the fact that the symptoms seem to proceed from disorganization of the autonomous system. "Falta, Eppinger, and Rudinger, assume a polyvalency of the thyroid secretion, and they regard the hyperthyroidism of Graves' disease as the outcome of a simultaneous though probably independent stimulation of both the sympathetic and autonomous nervous systems."[6]

There seems to be little doubt that tachycardia is only one of the many symptoms seen in this disorder which can be justly attributed to the sympathetic nervous system. We shall refer to these later.

The symptom which merits consideration next is the local enlargement of the thyroid gland. Although not so constant as tachycardia, it is nevertheless present in the majority of cases of this disease. The thyroid is generally moderately enlarged, the right side being perhaps more so than the left. In some cases, however, the enlargement is scarcely perceptible, while, on the other hand, it may be very great. In the early stages the gland is soft and elastic from vascular engorgement, but later it becomes harder from fibrous hyperplasia.

Histologically the gland presents a picture of diffuse enlargement, with a great increase in the vascular supply. There is definite new formation of tissue, which runs hand in hand with certain retrogressive processes, notably cell desquamation. Young follicles are seen associated with older cells, and in the latter may be seen breaking-down processes. As a rule a thrill can be detected, certainly in the larger tumours, and as the disease progresses the thyroid may alter in size, diminishing in favourable cases. It is said that the histological appearance in Graves' disease is typical, and Erdheim maintains that the young cell formations with fat granules are characteristic of Graves' disease.

For a long time the proptosis was looked upon as an essential feature of this disease, and it is only recently that we have come to realize that it is by no means always present. Its origin or, rather, the changes which underlie the exophthalmos are still unknown. It has been suggested that it is due to a deposit of fat behind the eyeballs; to a venous congestion in the posterior part of the orbit; to dilatation of the retrobulbar arteries; or to contraction of Müller's muscle. It is pointed out that the sympathetic system is largely connected with the symptoms of this disease, and that a disorganization of this system will account for many, indeed for most, of the features, always excepting the changes in the gland itself. On this theory it is much more probable that the proptosis is due to circulatory changes than to either a contraction of Müller's muscle or a deposit of fat in the orbit.

There are certain classical signs which one is accustomed to look for in association with the exophthalmos, and we must briefly refer to these. The widening of the palpebral fissure gives an appearance of great protrusion to the eyeball, and this is partly due to the retraction of the upper lid. This is known as Stellwag's sign. Although the eyeball in many cases appears to be prominent, it is in reality less so than it appears, on account of the uncovering of the eyeball due to the retraction of the upper lid. There is also a diminution of the reflex excitability of the eye, so that there is less irritation of the globe than would otherwise be the case. Another sign in connection with the lid is known as Von Graefe's sign, and consists in a lagging of the upper lid behind the globe during the downward descent of the eye.

Sometimes there is an insufficiency of the internal recti muscles of the eye, as a result of which convergence of the eyes in near vision is imperfect (Möbius). Occasionally blepharo-clonus is present.

Tremor is another constant sign of Graves' disease, and is quite characteristic. It is usually very fine, and confined to the hands, although occasionally it is seen in the muscles of the trunk, so that by laying a hand on the shoulder or trunk the observer can feel a quiver of the whole body (Oppenheim). The tremor of this disease is usually excited by movement or by nervousness, but is also present during rest. The rate of movement is somewhere about nine per second, and can best be seen when the patient extends the hands with the palms downwards.

Gatch has recently been investigating a test for hyperthyroidism, which was first suggested by Goetsch. The test consists in the injection of 8 minims of 1/1000 solution of adrenalin diluted with an equal quantity of sterile water. "A white patch surrounded by a red areola appears immediately at the site of puncture. After thirty minutes the white central patch assumes a bluish-grey tint, which in about two hours fades from the centre, and gradually colours the periphery. The bluish-grey areola thus formed persists for three to four hours if the test is positive and a definite degree of hyperthyroidism exists. In normal subjects the duration of the greyish areola is ephemeral; the degree of hyperthyroidism present is measured by the time which elapses before the areola disappears. Gatch has frequently found the test negative as soon as fourteen days after thyroidectomy, in cases where the reaction had previously been strongly positive."*

Before turning to the discussion of the menta changes present in Graves' disease, there remain a few less constant symptoms and signs which we have to mention. These may be classed under the headings vasomotor, secretory, and trophic. The subject of Graves' disease is very liable to suffer from profuse perspiration; indeed, in some cases this amounts to a definite hyperidrosis. As we stated in the previous chapter, these patients feel the heat greatly, and naturally this symptom is worse in hot weather. The sweating may be more or less local, or it may be general. One point of interest in this connection is with regard to the electrical resistance of the skin in cases of Graves' disease. Vigoroux first discovered

* Editorial, *Medical Press*, April 7, 1920.

that in patients suffering from exophthalmic goitre the resistance of the skin to electricity was diminished. This is now generally believed to be due to the undue moisture of the skin owing to the increased sweating.

Flushing of the skin, quite irregular in distribution, erythemata of a patchy nature, pigmentation—particularly of the margins of the lids of the eyes, and sometimes almost as marked as that seen in Addison's disease—are all phenomena of this condition. As is well known, there is a tendency to loose evacuations of the bowels, sometimes to actual diarrhœa; while the secretion of urine is also increased. The digestive system is often upset, and attacks of sickness, with bulimia, or, alternatively, loss of appetite, are about equally common.

The reflexes are often altered—more usually increased, although they may be diminished, or even, in rare cases, absent.

Cases are occasionally encountered in which the symptoms present a strange combination of those seen in exophthalmic goitre and those characteristic of thyroid deficiency. Thus, patches of lipomatosis are sometimes met with in a typical case of Graves' disease; while occasionally the condition of the skin approximates much more nearly to that typical of submyxœdema. Leonard Williams believes that there is often, if not always, a combination of excess and deficiency in this disease. Again, some of the symptoms which we are accustomed to regard as indicative of disease in the chromaffin system, such as pigmentation, would suggest the presence of a combination of thyroid and adrenal disturbance; and we have already said that many of these symptoms are more suggestive of adrenal than thyroid disturbance. The point to remember is that the symptoms and signs will vary according to the stage of the disease; so that if we encounter a case in the earlier or sthenic stage we shall find signs present which will not be there in the later stages. This point helps us to understand those patients who present some signs of over-action of the thyroid, and synchronously exhibit indications of hypothyroidism.

But as important, or nearly as important, as the physical symptoms of this complaint is the mental change which characterizes exophthalmic goitre. The main features of the sufferer from this disease are well known, but perhaps a brief sketch of the mental make-up of the patient may be useful. Whatever is the agent at work in these cases, whether the disturbance is originally in the sympathetic system, or to be attributed to an excess of thyroid secretion due to a cause or causes unknown, it is one fraught with evil for the peace of mind both of the patient and her relatives. From being gentle and docile, it may be, she changes to an intractable, selfish, restless, and inconsiderate being. The medical attendant as a rule receives the full benefit of this, and little he can do is right. He is either old-fashioned when he explains that the reason for rest in bed, for example, is to avoid straining an already weakened heart; or an ignoramus if he insists that rest combined with hygienic principles offers the best hope for alleviating the disease. If he suggests trying a new remedy, he is experimenting with her; if he persists with the old, he is a " stick-in-the-mud."

Perhaps the saddest of the changes wrought by this disease are the changes for the worse in the psyche, and it behoves the medical man to be very tactful with such patients, and to remember that the mind is the victim of a disordered bodily functioning and is no more to blame for its vagaries than the victim of, let us say, puerperal mania.*

The mental symptoms are, like the physical, capable of entirely clearing up; but even so, Leonard Williams doubts whether the individual is ever quite the same again. There can be little doubt that this disease plays havoc with the patient's character. It changes the quiet to the restless, the unselfish to the self-centred, and the amiable to the perverse. That these patients are notoriously difficult to treat is well known; that they make the treatment of their condition doubly difficult by their attitude to what is being done for them is almost equally well realized by every-one connected with the case except the patient herself.

Apart from the changes in character which we have outlined, more serious symptoms are seen in connection with Graves' disease. Apart from actual insanity, such as melancholia, mania, hallucinatory confusion,

* For a fuller discussion of the psycho-physical disturbances of Graves' disease see Chapter XI., p. 232.

and obsessions, there are the minor changes which are apt to lead to these more serious psychoses. Thus, the patient is excitable, wildly restless, sleepless, and confused. She is incapable of organized thought, of successful memory, or of attentive control; while her general mental habits have been well described by Reynolds as "mental chorea." It is quite obvious that it may be but a short step from this stage to that of insanity.

Needless to say, fortunately only a relatively small percentage passes from the mentality characteristic of Graves' disease to that typical of insanity. Nevertheless, the picture we have drawn of the mental condition of these sufferers is not exaggerated. It is true that in many diseases which the physician is called upon to treat to-day the patient's worst enemy is himself; and in no disease is this more true than in exophthalmic goitre. Consequently, it is no rare occurrence for such a patient to pass from one doctor to another, giving no one a fair chance to improve the patient's condition. This is the analogue in the mental apparatus of the restlessness in the physical system which prohibits the patient from resting, which is the one thing most to be desired. Thus is her temperament at the time her worst enemy, and it is this which needs treatment quite as much as the syndrome of symptoms which we have been discussing.

Such, then, is the bare outline of what constitutes Graves' disease. What is the prognosis, and what can we do to benefit that part of suffering humanity afflicted with Graves' disease?

Prognosis.

First as to prognosis. The course of the disease is very variable; it may in rare cases be rapidly fatal, or it may linger for many years, sometimes showing improvement, at other times retrogressing. Mackenzie gives the mortality at approximately 25 per cent. In patients who eventually recover, there is often a period when no improvement seems to take place and the disease seems to be stationary. Even in these cases there is a prolonged convalescence, and sometimes years afterwards some slight trace of the disturbance can be found.

In the early stages the malady is very liable to be diagnosed wrongly, some such diagnosis as neurasthenia being made. This probably partly accounts for the advances which this disease makes in the early stages, owing to a misconception of the nature of the trouble. Also the prognosis must be based upon the length of duration of the disease, the prominence of individual symptoms, the means of the patient, and, last but by no means least, the degree of mental abnormality which exists.

But, speaking generally, patients who have had the disease for a long time, especially where treatment has been of little avail, are not the most hopeful of subjects, and there seems little reason upon which to base hopes of complete recovery. Indeed, in such cases as these it is doubtful whether they are ever entirely restored to the *status quo ante*. Although it is usual to see amelioration of the symptoms, even a vanishing of the proptosis, or at least a diminution of the amount of protrusion under successful treatment, such patients are extremely liable to relapse. Their nervous symptoms recur from time to time; indeed, it would seem that it is very difficult for them to return to the successful functioning of this system once Graves' disease has developed.

There have, however, been many reports of recovery of long duration. Cheadle reports recovery lasting twenty years; while Oppenheim says that, in one case of his, recovery lasted "for twenty-seven years, in another for eighteen, in four for six to eight years."[7] The chief difficulty lies in keeping up the faith of the patients, in exacting obedience, and in counteracting individual symptoms.

Sudden death has taken place during the course of this disease, and when we remember the strain upon the circulation, the dilatation of the heart, and the disorganization of the neuro-musculature of this organ, it is not to be wondered at. Sometimes, as a sequel to this malady, atrophy of the thyroid may take place, with resulting myxœdema.

Treatment.

We shall have to refer at some length to the treatment of this malady, for it necessitates a discussion of methods which have been utilized for many years, as well as those which have found favour recently.

Modern physiological research has enlightened us upon many points in this connection, and some of these have indicated different methods of treatment, a few of which, at any rate, have shown signs of success.

It will be readily understood that the treatment of Graves' disease is no easy matter; for we have to contend with a condition the underlying pathology of which is not definite, and with a patient whose mentality renders curative measures more difficult than they need be. As we shall see later on, the various methods recommended range from local applications to the thyroid gland to psychological treatment—*i.e.*, psycho-analysis. The practising physician has, therefore, to consider from which of the many remedies we shall presently enumerate he will choose his weapons. At this point we shall consider the general treatment, and at the close of this chapter will be found a summary of the methods in use.

The resemblance between a neurosis (in this sense a functional nervous disorder) and many of the symptoms of the disease under discussion has already been referred to. A good working rule in the initial stage of the treatment of any disorder—more especially one without a specific treatment—is to remedy any abnormalities present, even if they have no apparent connection with the disorder. This rule is a particularly sound one to follow when commencing the treatment of a disorder such as neurasthenia, and equally so when first initiating the treatment of exophthalmic goitre.

To commence with, a careful scrutiny may reveal signs of oral sepsis which, even if secondary to toxæmia arising elsewhere, nevertheless requires treatment. There may be—in the present writer's experience there frequently are—indications of gastro-intestinal disturbances, a furred tongue, bad breath, offensive sweat, sallow skin, and local disturbances of digestion. It may be argued that these are an integral part of the disorder, and nothing more than secondary manifestations of an underlying disturbance; but it is equally likely that the toxins generated in the bowel have disturbed the endocrine balance and produced the thyro-adrenal disorganization to which we have already referred.

In any case the gastro-intestinal condition, whether it be primary or secondary, requires treatment, and this should be initiated from the commencement.

The frequency with which attacks of diarrhœa are encountered in these patients and the ease with which disorders of digestion are produced points to an abnormal intestinal condition. The presence of indicanuria is likewise suggestive, and the frequent and progressive loss of weight is a further proof of malassimilation. A form of diet should be selected carefully, and insisted upon. It is not easy to lay down definite lines of diet, but, speaking generally, a diet largely composed of dairy produce and fresh vegetables and fruit, with no butcher's meat and little fish or poultry, will be found to suit many patients.* It may be that the bacteriologist can help the clinician here,

* See footnote to p. 26.

by investigating the nature and character of the fæces; and there would certainly seem to be indications for withholding flesh food, where the adrenals are over-stimulated.

Plenty of milk, cream, butter, cream-cheese, brown bread, fresh fruit, salads, and uncooked vegetables, form a pleasant, nutritious and innocuous diet. If steps are taken to aid digestion and to disinfect the intestine (where there is evidence of intestinal indigestion) we have laid down a basis of treatment upon which a more detailed structure can be built.

Another point upon which emphasis must be laid *ab initio* is *rest*, and, as we know, this is the point usually disputed by the patient. But there must be no weakening on the part of the physician, for so long as the loss of weight and strength is progressive, and the tachycardia is in evidence, everything must be done to protect the patient from increasing the katabolism and further hurrying the heart.

The present writer is unable to dogmatize about the matter to which reference has already been made—namely, the value of psycho-analysis in the treatment of Graves' disease. Of one thing there is no doubt, that psychotherapy, in its widest sense, is of inestimable value in any disease where the symptoms are largely coloured by disordered emotion; and the one under discussion is no exception to the rule. But we need say no more on this subject, for we are all familiar with the results which can be achieved by judicious psychotherapy, whatever variety of disturbed functioning is concerned.

Many of the therapeutic measures in use for this disease are obviously secondary in importance to the main points just detailed. For instance, the administration of such drugs as the bromides, belladonna, aspirin, the salicylates, and so on, are purely empirical in their conception, and cannot do more than alleviate. The application of ointments to the thyroid gland, and more recently of the X-rays, is nearer a physiological antidote. But these measures, and indeed the surgical removal of part of this gland, can hardly be based upon sound medical reasoning, unless we believe that ebullition of the thyroid is the starting-point of the condition, and that the hyperadrenia and its sequelæ are secondary. We have already seen that in cases which reach the third or exhaustion stage the thyroid and adrenals are drained, and the condition is then one of hypo-adrenia and hypo-thyroidism. Any attempt to regulate the internal secretions in Graves' disease, by modifying or removing some of the secretion from the thyroid, is only tackling half the problem; and although it may be necessary to check some of the symptoms in certain cases by methods such as these, we must always realize that in reality we are only taking up the disorder from one point, and that this must necessarily be so, until we can establish that the thyroid is the *fons et origo mali*. So long as there is evidence that the adrenals are over-active, then we must bear this in mind, and not concentrate solely upon the thyroid.

But whatever treatment we may initiate—whether we incline to the old practice of counteracting the symptoms by controlling the exuberance of the heart's action, by producing adequate sleep, by anointing the thyroid gland, or by countless other small attentions —one factor remains constant, and that is the insistence upon sufficient rest, even complete rest in bed in bad cases. The application of the principles of general hygiene cannot be insisted upon too firmly, for this should be the bed-rock upon which all subsequent treatment is based. The difficulty is that the restlessness which these patients so often exhibit makes this stipulation a difficult matter to enforce. Nevertheless, it is not so much a matter of the practice of medicine as of the practice of common sense which suggests this; for it must be obvious that exertion, particularly undue exertion, which is always followed, as it is in this disease, by an increase in the symptoms, must be wrong, and therefore in no circumstances to be considered. When tachycardia is present, as it invariably is, our first aim must be to reduce the work of the heart to a minimum, and in doing this to reduce the tachycardia. Even if the rate of the heart's action is not excessive, the patient must be made to take periodic rests in the course of the day. She should rise late and retire to bed early, resting after meals, and avoiding hurry and perturbation. Where tachycardia is a marked feature, and more especially where the signs of general debility with marked loss of flesh are evident, complete rest in bed is essential.

There can be little doubt, moreover, that these patients require every hygienic advantage which can be given them. Thus, where possible, they should reside in the country or by the sea, but not in too bracing a place. They should rest in the open air, lie in the sun for the greater part of the day, and attempt no exercise of a strenuous nature.

Although we have suggested that vegetables are suitable where intestinal toxæmia is present, it has been recommended that these should be omitted from the diet of the patient, on account of the iodine which they contain. In this connection Rendle Short says: " We see also that exophthalmic goitre is due to hypersecretion of the iodothyrin, as is proved by the artificial imitation of the disease by excessive thyroid feeding, by the excess of iodine present in the colloid in Graves' disease, and by the character of the histological changes. Thus, we have reason to expect good from partial removal, which has been very successful in the hands of Kocher, the Mayos, and others. It would be reasonable also to try the effect of iodine starvation by eliminating vegetables and ordinary tap-water from the dietary, and substituting for the latter the water of a goitre well. It is well known that exophthalmic goitre and parenchymatous goitre show a sort of geographical antagonism, and the effect of the water in reducing the amount of iodine for conversion into iodothyrin would be valuable."[8]

It must be borne in mind that parenchymatous goitre is supposed to occur owing to a deficiency of the iodothyrin, so that the thyroid hypertrophies in an endeavour to supply that deficiency. If, therefore, there is little of this element in the thyroid of sufferers from parenchymatous goitres, they may be helped by the ingestion of vegetables. The water of the well-known goitre wells is supposed to produce parenchymatous goitres by containing a substance which deprives the body of the iodine by forming a combination with it. In an effort to counterbalance the diminished output of iodine the gland hypertrophies. On this assumption, then, it is recommended to try the water on patients suffering from exophthalmic goitre, in the hope that the unknown substance in the water will utilize some of the excessive secretion of the thyroid.

Turning now from the consideration of the general treatment of this disease, we find a host of other remedies which have from time to time been recommended. Apart from symptomatic remedies, over the consideration of which we shall spend but little time, we have before us a choice of many drugs, both for internal and external application. Of these, preference seems to lie with belladonna, aspirin, the salicylates, arsenic, and iron salts (where indicated). As we have already said, Graves' disease is often associated with anæmia, and therefore some benefit may be expected by the administration of these latter salts.

Of cardiac tonics, some authorities prefer strophanthus, while others recommend digitalis and nux vomica. But the help which the physician may expect from these drugs is strictly limited to their local action upon tachycardia.

Leonard Williams has reported good results in several cases from the hypodermic or intramuscular injection of bile salts. The *rationale* of this treatment lies in the fact that it is well known that these salts circulating in the blood produce a sedative effect on the brain and a slowing of the pulse.

Of recent years more and more stress has been laid on the chance of finding an organo-therapeutic compound which will help to neutralize the excessive action of the thyroid. Extracts of the adrenals have been tried, as also the extracts of pituitary, the ovaries, the parathyroids, and the spleen. Unfortunately, these have not given good results, only the parathyroid holding out any hope in this direction.

But there remain several external remedies to mention, some of which have been stated to give really good results in some cases. Of these, the X-rays is very well spoken of when applied to the exterior of the gland, and it has been said on many occasions to have limited the exuberant activity of the thyroid. In the Bradshaw Lecture,[9] Hector MacKenzie describes in some detail the treatment of Graves' disease by the X-rays. He relates a case of this disease which, under R ntgen therapy, was converted into a typical case of myxœdema. In all, thirty-six treatments were given, extending over a period of four years. MacKenzie considers that a possible reason why treatment by the X-rays has not up to the present yielded better results is because it has not been persevered with for sufficiently long. In commenting upon this case, he says: "I have never before seen such a complete disappearance of the signs and symptoms of well-marked exophthalmic goitre as has taken place in the above case. I think one is justified in ascribing the cure to the prolonged X-ray treatment.

"My present views on X-ray treatment are: It may prove to be far the best means of treatment at our command. It must be applied in no half-hearted way. It must be persevered with, and in many cases continued for a long period. It is most likely to prove beneficial in cases where the thyroid enlargement is moderate and the patient is not so seriously ill as to necessitate confinement to bed. I think it may prove valuable in bringing about a retrogression of the remaining thyroid after hemithyroidectomy. I have not at present sufficient evidence to speak of its usefulness where the goitre is a very large one. It has seemed to fail, as other remedies do, in cases of a severe type and rapid course. The trend of present experience in respect of X-ray treatment is decidedly in favour of its further trial."

Again, galvanism and faradism, applied either to the gland itself or to the sympathetic in the neck, has been tried, sometimes with success. Or a compress of adrenalin applied to the goitre is a help in some cases. I have occasionally had good results in some patients from the application of a mercury ointment to the thyroid. A small portion rubbed in every night, associated with internal treatment, has on more than one occasion resulted in an amelioration of the symptoms.

Again, since 1884 preparations have been manufactured from thyroidectomized animals. Of these, the more important are "antithyroidin" (Möbius), "hæmato-éthyroidine," and "thyroidectin." Beebe has evolved a method of treating Graves' disease by an antiserum produced by the inoculation of a thyroid preparation in animals.[10]

It is too soon to speak of the results of this latter treatment, but its value is said to have been proved in a large number of cases.

Of other organic extracts, favourable results have been reported following the exhibition of pituitary gland; and in one case under my care the symptoms were markedly improved following several months of this treatment. Thymus gland has been utilized, either in the form of sweetbread or as tablets, in the former $\frac{1}{2}$ to 3 ounces daily, in the latter one to three 5-grain tablets.

Some observers, notably H. Campbell,[11] advocate the administration of calcium salts to patients suffering from exophthalmic goitre, and claim better results from treatment in which this medication is included than from any other treatment.

Many authorities speak very highly of the beneficial effects of X-rays, and claim that treatment by this method successfully counteracts the over-action of the thyroid; while some observers maintain that the X-rays should always be administered before an operation is finally decided upon.

With regard to the question of operative interference, there can be little doubt that it should be reserved for the grave cases only, and that it should only be performed after all other remedies have failed.

The medical man must insist upon hygienic principles as a *sine qua non*, and he, as well as the patient, must regard the disease as one requiring the tacit obedience which is given to the orders of the medical man in a disease such as pneumonia or typhoid. If this is done, the patient is prevented from straining an already overworked organ, and much possible mischief may be prevented.

Summary.

The methods of treatment may be classified into three groups.

1. *General Measures.*

These include the removal of sepsis, the treatment of gastro-intestinal disorders, the choice of a diet suitable to the individual patient, and the insistence upon rest.

2. *Internal Remedies.*

These may be classed under:

(*a*) Inorganic drugs.
(*b*) Organic preparations.
(*c*) Dietetic régime.

The inorganic drugs are mainly chosen for their symptomatic action: digitalis for its slowing action on the heart and its diuretic effect; aspirin as a sedative and where "rheumatic" pains are a trouble; belladonna, strychnine, the bromides, etc., where their help can be utilized to lessen a symptom. Of the organic remedies, pituitary, thymus, and the preparations from thyroidectomized animals, can be ordered; but adrenal substance is only likely to be helpful in the later stages where there is adrenal exhaustion.

Dietetic treatment will include the prohibition of vegetables and tap-water, the omission of meat from the diet in toxic cases of gastro-intestinal origin, and the attempt to promote assimilation by assisting the digestive functions.

3. *External Remedies.*

These include:

1. Applications to the thyroid and the sympathetic.
2. Surgical interference.

Ointments or solutions of drugs can be applied to the gland in the hope of lessening its activity. Mercury ointment, adrenalin solution, the X-rays, and galvanism to the cervical sympathetic, are among this group. Surgical treatment includes ligature of the superior thyroid arteries, and removal of one lobe of the gland. A combination of these methods has been recommended by some surgeons.

In conclusion, we must emphasize the fact that, of all diseases which the medical man is called upon to treat, probably no one makes such calls on his perseverance and patience. For he has to treat an irresponsible patient, and one who is not the best judge of her condition. He requires infinite tact and an everlasting patience if he is to see the fruits of his labours. Furthermore, he must perforce try any remedies which hold out a chance of help, and he must discriminate nicely between those which are logically futile and those which are based upon reason.

There is some ground for hoping that in the near future, as our knowledge of the disease and its causation widens, we shall evolve a more satisfactory mode of treatment. For the present we must make up by our resourcefulness what we lack in our nicety of knowledge.

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CHAPTER IV

THYROID DEFICIENCY

In the previous chapter we dealt with the disease variously known as "Graves' disease," "exophthalmic goitre," and "hyperthyroidism," and showed that there is strong evidence to support the view that the symptoms are largely caused by excess of the thyroid secretion. In this chapter we propose to discuss thyroid deficiency, laying emphasis on the lesser degrees.

The history of thyroid-therapy has already been given, and we have described the earlier operations of Kocher upon the thyroid, and referred to the condition of "cachexia strumipriva" which was liable to ensue. Likewise we have mentioned the earlier work upon the functions of this gland, and the discovery by Gull and Ord of the disease myxœdema. Reference was also made to the important fact elicited by G. R. Murray, that this condition yielded to the administration of extract of thyroid gland.

The discovery was of the greatest importance, and for two reasons: First, because it proved beyond question that the peculiar disease to which the name "myxœdema" had been assigned was largely due to a deficiency or absence of the thyroid secretion; second, and even more important, it enabled complete relief to be afforded to the unfortunate sufferers.

Since that time a great deal of work has been done on the thyroid, both by laboratory workers and clinicians, with the result that myxœdema has emerged from the nebulæ of ignorance, and has taken its place as a curable disease.

But quite recently workers in all fields of medicine have been observing cases which, while they were by no means comparable to myxœdema, were sufficiently similar to appear to resemble this condition in certain points. As a countenance reminds one of a more familiar face by reason of a similarity in one feature, so do these cases, sometimes because of an item one can barely specify, make one think of the more marked disorder.

In this chapter, then, we wish to include those cases whose vagueness is a defiance to conclusive diagnosis, as well as the more definite disease which has received the name of "myxœdema." As we have already in a previous chapter discussed "cachexia strumipriva," we shall here confine our attention to that variety which arises apparently idiopathically, and not ensuing after operative procedures.

Myxœdema.

We will briefly review the features of this condition, but will not attempt to describe them in any detail, as they can be found discussed in any textbook of medicine.

As we have already said, Gull and Ord, G. R. Murray, Kocher, Mayo, and others, are the workers responsible for unearthing the cause of the symptom-complex which is known as myxœdema, and to Murray belongs the credit of discovering that the administration of thyroid extract relieved the symptoms.

Myxœdema is one of those interesting clinical conditions which are diagnosed rather by the summary of the effects produced by the individual symptoms than by one predominant feature. Thus, we find that a typical instance shows to the observer a slowly-moving, mentally sluggish, and prematurely aged individual, with localized deposits of fat, more marked in certain areas, a dry, rough skin, characteristic facies, and uncertain gait. The patient is altered in most ways; indeed, the disease, in common with many, if not most, of the serious disturbances of the endocrinous glands, changes the personality of the patient almost beyond recognition; but this alteration is, in the majority of cases, gradual.

The onset of the disease is insidious, and may occupy several years, although in a few instances its onset is more acute. The initial symptoms vary in different cases, but most usually commence with lassitude, debility, disinclination for exertion, and marked susceptibility to cold and chills.

The patient appears a changed man, and, to anyone who has not seen him for a protracted period, almost a different being. He becomes much stouter, and the actual body-weight is increased, but the fat is deposited in a characteristic manner. Pads of adipose tissue are situated in the clavicular regions, over the cervical spinal area, and in the neighbourhood of the lower ribs and flanks. But perhaps the facies is even more characteristic. The eyelids are thickened, with resilient bags of fluid under the lower lids; the lips, ears, and tongue, are enlarged; and the whole appearance of the face is one of extreme coarseness. At the same time there is an absolute lack of any intelligent expression in the face; the features are immobile, with, in some cases, a slight expression of surprise, owing to the eyebrows being somewhat raised.*

The skin loses its normal moisture, and becomes harsh, dry, and rough. The teeth are frequently in a state of decay, the nails are ridged, and the hair loses its gloss and shows evidence of trophic change—in fact, the epidermal appendages undergo atrophic degeneration.

The individual becomes comparatively lifeless. His extremities change; his hands are carried in a peculiar manner, which has received the name of "spade-hands," while his feet enlarge (not, however, in a marked manner, as is seen in gigantism), and are carried in a clumsy manner. Even the fingers show a change, for they are shaped somewhat like sausages, and are not narrower between the joints as are the fingers of a normal person.

* In "The Expression of the Emotions," Darwin draws attention to the curious fact that cretins never weep. They may cry out or moan, but do not, it appears, shed tears.

Small warty growths are liable to appear on the surface of the skin; while patches of dry eczema, similar to psoriasis, make their appearance.

The changes in the habits are equally characteristic. The speech is slow, and a long time elapses before an answer is given to a question. Co-ordination is interfered with, and the gait is "waddling." The mental attitude is almost exactly antagonistic to that which is typical of exophthalmic goitre. Thus, the patient is slow in every act, whether this act involves mental or bodily exertion. The finer co-ordinations of the muscles are deficient, a greater length of time is required even for simple acts, while the mental hebetude is shown by the set and unintelligent expression of the face.

This disease depends upon an atrophy of the thyroid gland, which can be demonstrated by an examination of the gland in the neck. It will be much harder to localize than in health, and to the examining finger its presence can only be detected by requesting the patient to swallow.

That the disease owes its origin to an absence or diminution of the thyroid secretion there can be no doubt; for the administration of an extract of this gland removes, or markedly lessens, the symptoms.

Lesser Degrees of Hypothyroidism.

Now let us turn for a moment to the study of the lesser degrees of deficiency in thyroid output, and we will then consider the physiological effects which the thyroid produces upon the body.

Needless to say, it is a more difficult matter to deal with these lesser degrees than it is to diagnose those marked instances known as myxœdema. There can hardly be any mistaking a case of myxœdema, unless a particular instance is very atypical. Once a typical instance is seen, the peculiar characteristics cannot well be forgotten. When, however, we come to describe the symptoms and signs which would lead us to arrive at a diagnosis of hypothyroidism, the difficulty arises that the various signs are widely divergent (according to modern views), and that their presence at all may be transitory, or, again, the physical signs may be very few. We shall endeavour to describe those signs which are usually present in a case of submyxœdema, laying especial emphasis upon those which are characteristic. In this way it is hoped that those cases requiring thyroid medication will be more readily recognized.

As is to be expected, on the whole the clinical picture is a modified version of myxœdema, with this difference, that the disease—*i.e.*, the thyroid deficiency—is still probably in its youth, and the more advanced changes, which are dependent upon structural alterations of the grosser kind, are absent.

It is not possible with our present knowledge of this subject to do more than hazard a guess as to the cause of thyroid insufficiency, and this we have already done.[1] Whether prolonged illness on the physical side, and anxiety on the mental, are capable of initiating a thyroid disturbance we do not know for certain. With the evidence at our disposal, it would seem probable; for, in the experience of most medical men, hypothyroidism is more liable to ensue after illness, worry, and similar harmful processes, than it is to arise spontaneously.* Whatever its genesis, it behoves the medical man to be on the lookout for its signs, more especially after acute illness. Let us briefly review its features, and outline the signs of thyroid insufficiency. Before doing this, however, it it better to state that there is a certain difference of opinion as to what constitutes the typical picture of thyroid insufficiency. We shall, therefore, at this place confine our remarks to those signs about which there can be little dispute, and in conclusion we shall

* I described a case of submyxœdema in a young male subject in the *British Medical Journal* for June 20, 1914. This followed a prolonged period of financial stress on the Stock Exchange, and was quite typical in its features. The patient was a young man, who had been out of sorts for some weeks, and had gone about his usual occupations, although he had noticed that he had been putting on weight rapidly. Briefly, his symptoms consisted in dyspnœa on exertion, bradycardia, eczematous rashes, pads of fat in the clavicular region, subnormal temperature, slow pulse, and trophic changes in the hair. Even the "eyebrow" sign was present. This man was first treated with cardiac stimulants, rest, and general hygienic measures, but made no progress. The day after he commenced thyroid medication the temperature approximated to the normal, the pulse-rate increased, he became more comfortable in himself, and after three weeks' treatment his good health was restored, with a reduction of weight. As may be imagined, his temperature chart was most instructive.

discuss the many points in this connection about which opinion is unsettled.

Signs of Thyroid Insufficiency.

When studying the main features of Graves' disease, we saw that the rate of bodily metabolism was vastly increased, that the nutritive exchanges were accelerated, and that there was a loss of weight in consequence. Again, we noted that the vasomotor system was irritable, that perspiration was easily induced, erythemata were frequent, and that the tendency to the production of glycosuria was increased. The general picture of thyroid insufficiency is exactly opposite (I am speaking of the main features) to that seen in exophthalmic goitre. Let us take the salient points one by one:

Temperature.—In this condition the bodily temperature is usually subnormal, in extreme cases as low as 96° F., more generally about 97° to 97·5° or 98° F. In any case, if the temperature be taken consistently, it will rarely be found to be normal. In this connection we must remember that these patients feel the cold in a marked manner, and are in a more or less constant state of chilliness. A patient who constantly complains of his "bad circulation" should be suspected of thyroid inadequacy.

Pulse.—The pulse-rate in submyxœdema is consistently slow, although I am aware that many authorities differ from this. I would therefore modify this statement by saying that, where other signs of thyroid insufficiency are present, and the pulse-rate is not slower than normal, or even faster, this is a sign that the condition present is not one of simple thyroid inadequacy, but is a condition of complicated endocrinous disturbance—a condition in which there may be more or less concomitant disturbance of the thyroid and some other internal secretion, or in which there may be a concurrent hypo- and hyper-thyroidism.

General Nutrition.—In submyxœdema, just as in the larger disease, there is a storage of products of digestion, as is seen by the larger amounts of sugar which can be consumed before glycosuria is produced. The bodily weight is therefore increased, but the deposit of fat is more or less local, as in myxœdema, and certain areas are more affected than others. Thus, the neck and shoulders are thickened, the clavicular regions contain pads of fat, while the feet and hands, ankles and thighs, are often found to be unaffected. Again, the hypochondrium is another situation which increases in size, while the abdominal wall frequently contains masses of fat.* A sudden increase of weight, without obvious cause, should make us at once suspect some thyroid disturbance.

* The condition known as "chronic subcutaneous fibrosis," about which Stockman of Glasgow has written, although not attributed to deficient thyroid secretion, nevertheless yields to the ingestion of thyroid extract. This condition is characterized by the increase of fat, but in the subcutaneous tissue are also found masses of fibrous tissue, and the latter tissue in this complaint is very tender to the touch.

Skin.—The skin is dry, rough, patchy in places, and may be in an eczematous condition. The internal surfaces of the tibiæ, the sternum, the forearm, and the back, are the main situations where ichthyotic rashes are seen. There is usually present in thyroid insufficiency an itching, which is sometimes so intolerable as to make the patient wish to scratch every part of his body at the same time. There may, on the other hand, be little or nothing to see, but the proof that the skin irritation is due to the diminution of thyroid secretion is that it gradually yields when thyroid feeding is instituted, although not until some time after the beginning of the treatment. If the hair be examined, it will be found to be dull and without its usual lustre, sparse in places, prematurely grey (in cases where the condition has persisted for some time), with patches of alopecia. Léopold-Levi and H. de Rothschild draw attention to the "eyebrow sign"—*i.e.*, the scarcity of hair in the eyebrows, with a marked diminution of the outer third of each eyebrow. This sign the present writer believes to be fairly constant, as he has observed it in many patients showing other signs of thyroid deficiency.

Constipation.—The subjects of this condition are nearly always constipated. As in thyroid excess the reverse is the case and the motions are on the loose side and frequent, so in submyxœdema are the bowels costive.

Other Characteristic Features.—If we can describe a type of "thyroid deficients"—that is to say, subjects of long-standing submyxœdema—we must lay emphasis on one or two points. The individuals are usually small, with deepset eyes, scanty hair, dry skin, and with the appearance of premature senility. They require abundant sleep, and are particularly liable to somnolence after meals.

They are inclined to obesity, with the deposits of fat which characterize this condition, thickset, with an expressionless face, possibly carious teeth, and gingivitis or actual pyorrhœa.

Again, the subjects of thyroid deficiency are very prone to fatigue, which developes without an undue expenditure of energy. In this way they resemble the neurasthenic, just as in their somnolence after food they remind the observer of the lithæmic subject. As we pointed out in a previous chapter, these patients frequently exhibit signs of premature senility, the arteries may be thickened, the skin wrinkled, the joints have lost their suppleness, as they are wont to do in old age. We may refer in passing to the supposed relationship between the parathyroid glands and calcium metabolism, as it is assumed by many observers that derangements of these small glands permit the retention in the body of the lime salts, which are deposited in various parts of the body. It may be that thyroid deficiency is associated in many of these patients with a parathyroid deficiency, and that it is the diminution in the latter secretion and not in the former which causes the symptoms of premature senility.

It may be helpful at this stage of our study to refer to the work of Léopold-Levi and H. de Rothschild on this subject. These observers combine physiological research with clinical utility, so that the two aspects of thyroid deficiency are, so to speak, brought into focus.[2] These authors refer to "thyroid instability"—*i.e.*, to the liability to disturbance in the normal working of this gland, whether in the direction of excess or that of deficiency. They assert that a simple excess (slight hyperthyroidism) is very liable to be succeeded by a deficiency, and that the two conditions—hyperthyroidism and subthyroidism—are frequently associated in the same individual. Thus, when these two conditions are present in the same patient, the prominent features of both might equally well be noticed. Those pointing to excess of the secretion of the gland, such as palpitation, nervousness, exophthalmos, and tremors, are combined with those indicating deficiency, such as constipation, chilliness, sclerodermia, scanty hair, etc. In another place[3] Léopold-Levi refers to the "hyperthyroidism associated with thyroid deficiency," which he says may be classified as follows:

(*a*) Paroxysmal derangements of a hyperthyroidic nature, which appear as simple reactions and may be classed as symptoms.

(*b*) Reactions of a more complex nature, the manifestation of which includes other symptoms, and which may be classed as syndromes.

(*c*) Reactions affecting the thyroid gland itself (endogenous goitre).

To emphasize the characteristics which we have already discussed as being present in thyroid deficiency, we will quote from this same article what this author gives as being the symptoms of a "slight degree of hyperthyroidism," as by this means we shall serve to impress the two different clinical pictures.

"1. Hypertrichosis, more particularly of the eyebrow.

"2. Hyperthermia, flushings, febricula of thyroid origin.

"3. Acro-erythrosis, with cutaneous humidity.

"4. Tendency to diarrhœa, the stools being soft and frequent.

"5. Great physical restlessness, with a sensation of being hurried.

"6. Insomnia.

"7. Emaciation.

"8. Excessive height.

"9. Developmental precocity.

"10. The syndrome which I have named 'syndrome of persistent juvenility.'

"11. Extreme nervous irritability, with cardiac and cutaneous excitability, etc.

"12. Large brilliant protruding eyes, with nystagmiform movements.

"13. The reactions are generally excessive, and there is exaggeration of the nutritional exchanges.

"14. Hyperplasia of the entire thyroid gland."[4]

It is, however, quite obvious that many of these symptoms can only be present in those patients where the condition has been congenital, has commenced during adolescence, or has been in existence for a very long time; for, to take only one example, the stature could scarcely be altered in an adult patient who developes the condition after, let us say, a severe illness. But, on the other hand, there can be little doubt that many of the symptoms are quite constant, and can be observed in a large proportion of cases. At the present time the writer of this book has under his observation a lady who is undoubtedly suffering from deficiency of the thyroid, but has also the syndrome which points to excessive action of this gland. Thus, while she has typical deposits of fat, ichthyotic skin, characteristic hair, somnolence, and mental turpitude, she also has slight tachycardia, rather prominent eyes, an almost unnoticeable tremor, some degree of nervousness, and transitory restlessness. In fact, in this case the picture changes from time to time—sometimes the signs of excess in the thyroid secretion being uppermost, at other times the signs of deficiency being more noticeable. There can be little doubt that in many cases both conditions are present, but not necessarily at the same time. It is quite possible that a hyperthyroidism succeeds a transitory deficiency, that while this condition is present the signs of its presence are marked, but that the reaction brings with it exactly opposite symptoms.

The view expressed by Léopold-Levi—namely, that the thyroid can be in an unstable condition, so that both these two opposite syndromes can be combined —is one which is supported by many observers. He believes, however, that the two conditions are rarely combined at the same time, but that the fundamental state is one of "thyroid instability." This, however, may constitute a condition in which the thyroid wobbles, so to speak, between outbursts of hard work and spasms of idleness. About such a state he says:

"Associated with thyroid insufficiency is a large number of syndromes, the characteristic features of which are that they are precipitated suddenly in the form of thyroid crises, and that they yield to treatment with thyroid extract.

"Although associated with thyroid inadequacy, these syndromes are the clinical expression of a hyperthyroidism which is, in itself, the reactionary manifestation of the fundamental subthyroidic condition.

"They are—migraine, ophthalmic migraine, asthma, nasal asthma, attacks of chronic rheumatism and gout, mucous enteritis, urticaria and other skin affections (acne, eczema), mental symptoms."[5]

From this quotation the reader will see that the alteration in the thyroid is believed, by this authority at least, to present many features which are sufficiently capable of recognition to enable the diagnostician to arrive at an accurate judgment. Before closing this chapter, however, it may be well to remember that not all these symptoms can be expected to be present in the same patient. Rather must the physician be on the lookout for any of them, remembering that, so far as the endocrinous glands are concerned, diagnosis must be aided by ingenious detection.

REFERENCES.

1 See Introduction, pp. 3-6.

2 See "La Petite Insuffisance Thyroidienne et son Traitement," by Léopold-Levi and H. de Rothschild, published by O. Doin et Fils, Paris, 1913.

3 *Practitioner*, vol. xciv., No. 2, p. 211.

4 *Ibid.*, vol. xciv., No. 2, p. 212.

5 *Ibid.*, p. 213.

CHAPTER V

THYROID DEFICIENCY (*Continued*)

We have now discussed the broad outlines of thyroid excess and thyroid deficiency. But this latter subject is of such importance, if we are to use to the full the powers which a knowledge of organo-therapy gives us, that we propose to devote this chapter to a more detailed study of the signs and symptoms of hypothyroidism.

Owing to the importance of this subject, which, indeed, increases from day to day as our knowledge of the lesions which may be attributed to disturbances in the hormonic system becomes wider, it is necessary for us to discuss at some length this aspect of the endocrinous glands. For thyroid deficiency is of the most vital interest to all students of medicine, if only that, when recognized early, many aberrations from normal health may be remedied, or even averted, by the administration of extract of the thyroid gland.

For this reason alone it behoves us to make ourselves *au fait* with the more marked symptoms of this disorder, for many of these will yield to rational therapy. Again, as in every other treatment, there is a right and a wrong way to proceed with thyroid administration, but, unfortunately, this fact is not widely appreciated. Probably from the erroneous impression as to the dosage which is given in text-books of medicine, and in posological tables, the dose of thyroid extract is usually far too high. In any case it is necessary to proceed cautiously when prescribing this drug, for the personal factor is never more important than in thyroid-therapy. We shall discuss this in more detail at the end of this chapter.

In the last chapter we reviewed the opinions which are held as to the symptomatology of thyroid deficiency, and quoted the views of Léopold-Levi and H. de Rothschild. We referred to "thyroid instability," to the syndromes which these authors believe to be characteristic of thyroid excess and thyroid deficiency, and to their belief that the two conditions may be present successively or even concurrently in the same patient. The opinions expressed by these observers are important, for they have made a careful study of the thyroid gland and its disorders, and their conclusions are of the greatest help to anyone wishing to familiarize himself with thyroid dosage.

Harrower quotes in his book on "Practical Hormone-Therapy" from Léopold-Levi and H. de Rothschild's book on "La Petite Insuffisance Thyroidienne."[1] These authors say: "Considerable importance attaches to minor thyroid insufficiency, for, unlike myxœdema, it is very frequent. It should be also especially interesting to the physician because of its usually rapid response to treatment. Clinical experience is the basis of these deductions, just as it was the original basis of the present knowledge of the stigmata of hypothyroidism."

Now, let us spend some time in studying those points which are generally considered to be typical of thyroidic insufficiency. We have already studied the main symptoms, and the manner in which normal physiological processes are altered in the absence or perversion of thyroid secretion. Our object now is to study the type which makes one look for symptoms rather than the symptoms themselves.

The following may be said to be points in bodily construction which suggest faulty thyroid secretion. As we have already said, these patients are small. Their stature is frequently diminutive, while the development of their soft structures is excessive in proportion. There is also present, according to Hertoghe, a relaxed condition of the articular ligaments, which permits of over-extension of the joints. Thus, we shall look for what is known in popular language as "double-jointed" people. The patient to whom we referred in the last chapter (in whom symptoms suggestive both of excess and insufficiency were present) showed this symptom remarkably well. She was able to bend her fingers back until the nails almost touched the back of the hand. In this connection, Hertoghe refers to a man who had been under his care for a number of years suffering from thyroid insufficiency, in whom there was spontaneous painless dislocation of the patella. So impressed is Hertoghe with the changes in this respect that he says "it is possible, with very little practice, to judge of the degree of thyroid inadequacy merely by squeezing the patient's hand."[2] He says that these hands give the impression, when squeezed, of a "glove filled with clay."

The present writer is certainly of the opinion that the relaxation of the ligamentous structures in submyxœdema is something more than an artificial symptom. He has noticed it in a number of patients affected with this disease, in which the diagnosis was confirmed by treatment.

Nevertheless, it must be remembered that, in describing a type of submyxœdema, we are only dealing with long-standing cases or with the individuals in whom there has been a deficiency since infancy. It is obvious that, where the disorder commences in adult life—for instance, after an infection—we shall not expect to see the signs of a type such as we have just described.

In children certain signs of thyroid deficiency have to be added to those for which one must look in an adult. Thus, while growth is impaired and stature infantile, we have learned to expect a protuberant abdomen, a lumbar lordosis, due to relaxation of the spinal ligaments, sometimes abnormalities of development, such as umbilical hernia, undescended testes, and so on.

Again, as such children grow up, they continue to show these and similar signs, which are more noticeable owing to adolescence. The sexual development is delayed, immature sexual organs only being present in many cases, the stature remains stunted, and there is faulty mental development. The exhibition of thyroid extract serves to increase stature, remedy faulty development in other directions, and even to abolish symptoms such as umbilical hernia. If omitted too soon, or if given in insufficient doses, the improvement is apt to cease and the growth to stop.

This, then, is what to expect in subthyroidic children; if exaggerated, we meet cretinism. Such children are deficient in hair, and may even show more or less generalized alopecia. This, when combined with the infantile expression of the face, should at once make one suspect thyroid deficiency. The child may be small for his age; he may present one or more of the stigmata referred to above; and, finally, the diagnosis is clinched by the exhibition of thyroid extract and the resulting improvement.

So much, then, for thyroid deficiency in a child. What produces this is a more difficult question. There can be little doubt that in many cases the tendency is an inherited one. These children often come from stock which can be shown, on careful examination and questioning, to be subthyroidic. Hertoghe quotes a case of infantilism of the Lorain type, the mother of the child being a myxœdematous subject of a benign type.

Like many other diseases, prenatal conditions must be blamed for many of these cases, and it will have already been noticed how some of the defects, due to imperfect development, are more or less directly traceable to the thyroid gland, as they are remedied after birth by the administration of the extract of this gland. In support of this, witness the umbilical hernia in one of Hertoghe's cases, and note how it cleared up when the child had been taking thyroid for some time. Again, it will be remembered that such stigmata as imperfect development of the bones are among the signs of inherited syphilis; while it has been stated that the administration of thyroid extract is as efficacious as iodide of potassium in healing tertiary syphilitic lesions.[3]

Two other functions of the thyroid are pertinent to our study. First, we have to remember the theory which deals with the "antitoxic" power of this gland, and to bear in mind that, if this is true, the subjects of any kind of thyroid deficiency must needs be more open to bodily infection, either from so-called autogenetic or heterogenetic sources. Second, as pointed out by Hertoghe, the life of each cell of the body, considered as an individual, is relatively a short one. It serves its purpose, degenerates, and is excreted from the body by one of the normal channels. For this to be performed, however, in a normal manner, the presence of thyroid secretion is necessary; for in its absence such cell elimination does not follow its usual course. Hence the vast increase in the subcutaneous tissue which is present in myxœdema, and to a less degree in submyxœdema. As is so well known, this gives rise to œdema, or, to be accurate, to increased subcutaneous tissue, which pits on pressure. Extract of thyroid gland diminishes this abnormal subcutaneous tissue, and in so doing lessens the bodily weight. The excretion of nitrogen is increased by this extract, so that the elimination of broken-down cells is restored to normal—another reason for the reduction in weight under thyroid feeding.

As we have said already, the submyxœdematous patient is habitually constipated, and this may have an effect to which we drew attention in a former chapter. These patients show many of the signs upon which Lane lays emphasis as indicative of intestinal stasis; in fact, one of these signs is atrophy of the thyroid. The question to be answered is this: Is the thyroid primarily responsible for the inertia of the intestine, or does this latter factor produce atrophy of the thyroid?

I have seen cases which would argue that Lane's view is the correct one; on the other hand, many patients impress one more in favour of the theory that the thyroid atrophy is responsible for the signs to which both the supporters of the alimentary theory and those who uphold the "primary thyroid deficiency" theory lay claim. A short time ago I saw a lady who was complaining of vague pains in the extremities, dry and itching skin, languor and lack of mental alertness, and constipation. On examination I found a swelling of the thyroid gland, a slow pulse and an ichthyotic condition of the epidermis. Furthermore, there was a good deal of evidence of intestinal stasis, such as meteorism, offensive flatus, insufficient motions even after a purge, and digestive disturbances. To many of those students who have read Sir Arbuthnot Lane's work upon the subject of intestinal stasis, the signs indicative of intestinal stasis were all (I refer to the main signs, and not to the smaller indications) present. At the same time the student of opo-therapy would find most of the signs which he has learnt to regard as pathognomonic of thyroid deficiency present in this case. The stature was small, the hair atrophic, the skin dry, the pulse slow, the bowels costive. I need hardly enumerate the other well-known signs.

Any observer dealing with functional disturbances is, however, bound to be struck with the frequency of intestinal disturbances in these patients. It may be said that constipation is an almost universal complaint, and that too much stress has of late been laid upon it as an etiological factor, and that its presence in the subthyroidic is secondary to the endocrine disorganization. This argument is, at least, open to question. If the thyroid functions as a filter, it is equally likely that, where toxins are, or have been, at work, we shall find a drying-up of the thyroid secretion.

There we must leave the discussion of the primary cause, as there is insufficient evidence to warrant us in dogmatizing further on the why and the wherefore of thyroid atrophy.

In reading the mass of literature which has accumulated of recent years on this subject, the reader is struck with the many different signs which are believed by the majority of observers of organo-therapy to be caused by thyroid insufficiency. Even if at first glance one is inclined to believe that the clinical picture of submyxœdema has been exaggerated, yet, if one realizes the signs which a severe degree of thyroid deficiency produces, one can scarcely doubt that a minor degree might very well alter the individual, although in a slighter degree; indeed, in the very mild cases to so small a degree as to make the change all but imperceptible.

The main object of this chapter is to bring the practical points in connection with hypothyroidism before the notice of those whose time does not permit of the perusal of the latest physiological and clinical research, so that a greater percentage of patients who might be helped by organo-therapy (and who will in all probability be helped by no other means) shall benefit by our knowledge, which has increased every year since Murray's original discovery. The study of the changes wrought in the various parts of the body by an absence or diminution in the secretion of the thyroid are so numerous that it will be best to deal with them separately, classing them under the different bodily systems. We will therefore study them in this way.

The Influence of the Thyroid Secretion upon the Cell.

Throughout life the living cell requires certain hormones if it is to follow the normal cycle of life. Thus, if starved of thyroid its growth is impaired; administer to the individual organism the extract of this gland, and growth is resumed. This is shown by the behaviour of cretins to thyroid feeding; they improve in every way under such treatment, but relapse if it is stopped or diminished. We have already pointed out that broken-down cells which should be eliminated are retained and stored (in a form that originally was thought to be mucinous) if the thyroid secretion is diminished. Thus, the cycle of growth and decay are both interfered with, if the endocrinous system is disturbed. In association with this, we must explain one or two important facts. The subject of thyroid deficiency is never "fit"; he is generally tired, he finds work a burden, and, whether his employment is physical or mental, he requires a "push" before he can make himself take up his tools. Again, his mental apparatus fails him, his memory is unreliable, he cannot recall either recent or past events; his attention wanders; his concentration is never at its brightest when he wishes to solve a problem; and, in a word, he is sluggish mentally as he is languid physically. He is neurasthenoid.

The muscular system, in association with the subcutaneous, ligamentous, and fascial systems, undergoes infiltration; while the nerve cell "suffers derangement of nutrition." It becomes "infiltrated, and it also undergoes compression, as the result of the infiltration of the connective tissue surrounding it. Hence, the transmission of motor and sensory impulses, both voluntary and involuntary, though delayed, is in no sense abolished. The reflexes are tardy, but they are present."[4]

Therefore the cells of the nervous system are embarrassed in a double manner—from within and without. The infiltration of fascia, of muscle, and of sheath, must of necessity exaggerate the difficulty of exertion. This would apply both to physical and mental exertion.

Symptoms Referable to Nervous Tissue.

Apart from the mental sluggishness, which we have already described, these patients suffer from a variety of ailments more or less directly referable to the nervous system. Thus, they are very liable to headache, which is usually frontal, but occasionally occipital. The two forms, however, are rarely merged. The headache of thyroid insufficiency is, in nearly every case, worse in the morning, improving as the day wears on.

Giddiness is another constant symptom, with which is associated, in some cases, a "swimming" sensation. Tinnitus aurium, either in the form of buzzing, roaring, whistling, or shrieking noises, is common, while these patients sometimes experience even more serious sensory disturbances, such as hearing voices, the ringing of bells, etc.[5] In practice, many such cases have been benefited by the administration of thyroid extract. So far as I am aware, there is no evidence that true vertigo is seen, although I have prescribed this extract for one or two patients in whom the giddiness and dizziness were very similar to true vertigo.

We have already referred to the functional nervous changes which are seen in thyroid deficiency, of which somnolence is, perhaps, one of the most marked. These patients seem to be able to sleep very soundly at night, after every meal, and at any other time when the opportunity offers. Most subthyroidics complain of their marked tendency to slumber at all times, and the more intelligent find that it is sufficiently marked to be abnormal. In spite of this, these patients do not wake up refreshed, and they feel worse in the morning than they do at night. Hertoghe suggests that "in all probability the thyroid neutralizes the toxins generated during the hours of activity during the night—that is, under normal physiological conditions—but that this does not happen in the subject of thyroid deficiency."[6]

We have already dealt with the changes in the mental apparatus which must be looked for in submyxœdema; to the confusion of mind and the lack of mental initiative we must attribute the slowness of thought, as well as the lack of confidence, which these patients show. To these facts also we must attribute the undue exertion which any work demands from these patients.

The Subcutaneous and Muscular Tissue.

The thickening seen in thyroid inadequacy is characteristic. It involves all tissue, according to most observers, but in certain areas it is laid down more or less in "heaps." Thus, the nape of the neck down to the last cervical vertebra shows a thickening, while in the last-named area is almost always seen a mass of fat which resembles a lipoma. Particularly is this so in adult patients, more especially in the female sex. The head is held somewhat forward ("cassowary neck"), so that the cervical deposit appears more prominent than is really the case. The shoulders of such patients are broad, while the clavicular regions contain pads of fat.

Such deposits of fat as these are more or less dependent on sluggish circulation, and therefore regions such as the abdominal wall are apt to suffer. The flanks and back are, in adult patients, enlarged by rolls of fat, while the bones of the extremities are sunken in an envelope of adipose tissue. This deposit is not solely fatty, nevertheless it adds to the body-weight considerably and hampers bodily activity. The entire subcutaneous integument appears to be thickened, and this thickening can be made to pit on pressure, although the pitting disappears as soon as the pressure is relaxed.

As regards the changes in the muscular system, we can by reason of these changes explain several symptoms from which these patients suffer. The muscles are burdened with fat and mucinous infiltration, so that their size is increased and their drainage insufficient. Muscular movement is hampered, so that the metabolic exchanges are even more restricted. Hence the dislike of active exercise which these patients invariably show. Again, the increase in the volume of the musculature leads to discomfort, if not actual pain, which latter may be vastly relieved by the exhibition of thyroid extract.

It is well known that children who are the subjects of thyroid inadequacy are very prone to the development of adenoids, and that this is one of the characteristic stigmata of this condition. Again, in such subjects the enlargement of lymphatic glands is common, and some thickening of these structures is frequently observed.

Sweating is practically unknown in submyxœdema, *per se*, and in consequence there is some increase in the secretion of the kidneys, with a tendency to nocturnal enuresis. The solids of the urine are, of course, diminished, but increase enormously when the patient is taking thyroid. The nocturnal enuresis from which these patients suffer is in part, at any rate, due to the extreme heaviness with which they sleep; and for some years now thyroid extract has been prescribed empirically for this condition, although the underlying causation was not understood in the same way as it now is. This medication has given very good results in many cases, but it is almost infallible where the underlying condition is one of thyroid inadequacy.

The absence of adequate secretion from the skin—and these subjects rarely sweat—results in a stagnant condition of the liver; and, according to Hertoghe, this results in itching of the skin, the icterus of myxœdema. It may also assist in the intense drowsiness, if not also in the slow pulse; but even if so, it would only be a contributory factor. It is, however, quite conceivable that the constipation is partly due to diminution of the normal biliary secretion in the intestine, the natural laxative.

The Osseous and Cartilaginous Systems.

The delayed growth resulting from a deficient thyroid secretion is too well known to demand lengthy description. So long as the epiphyses are not ossified, there remains the possibility of renewal of growth under thyroid feeding. This can be ascertained by the Röntgen rays.

Again, myxœdema produces its characteristic infiltration in the joints and their ligamentous structures. This causes crackling in the joints, and gives the impression of a rheumatoid condition. When this sign is present, therefore, a careful search should be made for other symptoms pointing to thyroid deficiency. It has been said that delayed union after fracture is very common in subthyroidic subjects, and that the bone unites on the exhibition of thyroid extract.

Epidermal Symptoms.

The dry, rough, and ichthyotic skin which characterizes these subjects has already been described. From their point of view, this is probably one of the most troublesome features, as the inconvenience of a generalized itching cannot well be exaggerated. There is little to be seen on examining the skin of these patients beyond what we have already described. The hair suffers in common with other epidermal appendages. The nails are brittle and grooved, or they may be actually cracked. As we have already said, the "eyebrow" sign, first described by Léopold-Levi and H. de Rothschild, is of considerable diagnostic significance. There is a sparseness of the outer third of each eyebrow, with a scarceness and partial falling out of the whole eyebrow. This feature can be seen in many subthyroidics, and should always be remembered when looking for confirmatory evidence of a suspected inadequacy of this secretion.

Pigmentation of the skin, perhaps more commonly seen on the forehead, and raising of the eyebrows, are both characteristic; while the lips are usually thickened, and the mouth tends to open. The changes in the facial characteristics give an unusually stupid appearance to the patient, but this changes under thyroid feeding. The more marked cases of thyroid insufficiency develope countenances which resemble nothing so much as a porker; and the change which is brought about in the expression as treatment proceeds is most gratifying to the patient himself, as well as his relatives and friends.

In adult subthyroidics the hair is prematurely grey, and this change in colour is usually more marked over the temples. In the case which I published in the *British Medical Journal* of June 20, 1914, this feature was well shown, although the patient was a young man about twenty-eight years of age. If the hair is a normal colour, it is frequently without gloss, and is brittle and "lifeless." Patches of alopecia are common, and the scalp as a whole is dry and scaly.

It must be remembered that pigmentation of the skin is seen in thyroid excess as well as in thyroid deficiency, and that it is a characteristic feature of Addison's disease.* As a diagnostic symptom, therefore, it is not of great value.

Sexual Symptoms.

During childhood the diminution or absence of the thyroid secretion prevents the normal development of the genital organs at puberty. In fact, such patients grow up to adult years without any change from the

* The bronzing characteristic of an adrenal deficiency disease—*e.g.*, Addison's disease—has its analogue in the brown pigmentation seen in submyxœdema. These stains disappear, in some patients, under thyroid medication. An instance of this is recorded in Chapter XIII., p. 298.

infantile character of these organs. Indeed, in some cases more serious defects are seen; for cryptorchidism, either complete or unilateral, may be present.* In cretinism, of course, there is no development of any sexual characteristics, and the child remains in this respect unchanged.

Graves' disease produces a diminution of the periods, either with scanty menstruation or amenorrhœa. The reverse is true in submyxœdema, for here there is a tendency towards menorrhagia, although the periods do not as a rule develope until the patient is well past the usual time. The uterus remains undeveloped, or at all events partially so, while the ovaries are likewise immature. There is sometimes a marked retroversion.

The changes brought about in thyroid inadequacy by pregnancy are for the best; while the patient is pregnant the thyroid secretion is increased. But, unfortunately, this improvement is not permanent, and she retrogresses, so far as this is concerned, after delivery. Immediately after delivery there is too much secretion, but later this ceases, and the former condition of subthyroidism is reverted to. According to Hertoghe, some of the increased thyroid secretion is directed towards establishing uterine involution, while another function of this important secretion at such times is to establish lactation.

* An interesting case in which delayed descent of the testes was treated with success by organo-therapy is recorded on p. 305.

Gastro-Intestinal Symptoms.

In considering the gastro-intestinal symptoms of thyroid inadequacy, we must refer again to the syndrome, which Lane attributes to intestinal stasis, but which observers in organo-therapy claim to be caused by the thyroid. "The symptoms are hypothermia, uncontrollable headache, rheumatoid pain and neuralgia, mental depression, dyspnœa, asthmatic attacks, premature greyness and baldness, dental caries, cholelithiasis, and brownish pigmentation of the skin." Thus Hertoghe refers to this syndrome, and he attributes the gastro-intestinal symptoms of thyroid insufficiency to infiltration of the muscular tissue of the intestines, causing partial paresis. This in turn leads to ptosis, or partial ptosis, and then we have kink formation and the other features so carefully described in Lane's book.[7]

We must emphasize, in passing, what we believe to be a very important aspect of this condition—namely, weakening of the abdominal wall, which fails to give that support upon which the intestines have come to rely. This may be due to degenerative processes of an infiltrative nature, or to some other cause, but in any case the weakening helps the intestinal derangements. This in turn affects the digestive functions; appetite, which is notoriously capricious in subthyroidics, is poor; digestion is imperfect, and assimilation lessened. These patients are always weak and incapable of sustained effort. This is probably due in part to the causes already enumerated, and partly to deficient assimilation of food.

The association between subthyroidic conditions and septic affections of the alimentary tract, such as appendicitis, has often been commented upon, while it is said that the relation between tonsillitis and appendicitis is a close one.

Rectal hæmorrhage is said to be common in this condition, and, according to Hertoghe, it is due to premature thickening of the rectal veins and to the deficient coagulation of the blood. Just as the monthly period is apt to be excessive, so is the hæmorrhage due to piles, etc., liable to be copious.

Treatment.

We have now outlined the main changes which may be observed in subthyroidic patients, and the chief signs by which the condition may be recognized. All that now remains to be done is to summarize our conclusions in a few words, and to outline the treatment.

Whether the condition is in evidence during childhood or not until after adolescence, the main features are characteristic. The change in the bodily temperature is constant (a subnormal temperature is nearly always present), likewise the pulse is slow. These two points should always be investigated. Having determined the condition of the temperature and pulse, the skin and hair should be examined, and a careful investigation undertaken to determine the bodily weight and the characteristics of the subcutaneous tissue. The deposits of fat, if present, are usually localized. On the other hand, the patient may not necessarily be obese if the degree of thyroid deficiency is slight. In such cases careful observation must be made to ascertain whether other signs are in evidence, and, if so, whether the sum of the signs and symptoms points to submyxœdema. The condition of the digestion and the bowels, the nature of the monthly period in women, the presence or absence of sensations of chilliness, of flushings, and of pains in the limbs, should be ascertained.

Having reached this stage in the investigation, the further points which suggest themselves for examination deal with the minor changes which are characteristic of this disease. Any change in the voice, in the expression, or in the mental outlook, which either the patient or her relatives have noticed, is of importance. The functional efficiency of the patient should be studied, bodily weakness and fatigability examined, and the patient questioned as to the length of time these changes have been noticed.

All the minor points are important, as the question of treatment depends upon these. We cannot emphasize too strongly the fact that, so far as submyxœdema is concerned, the initial dose should be small. Even if this should be so small as to appear to the inexperienced prescriber to be useless, it is infinitely preferable to order a small dose, and to continue this over a lengthy period, than to commence with a big dose and have to suspend treatment on account of untoward reaction.

In severe cases—*i.e.*, where definite myxœdema is present—the initial dose may be larger; but such cases do not nowadays form the majority of patients, as they are usually far outnumbered by the patients who show the signs of minor degrees of hypothyroidism. Where myxœdema is present, the patient may be given one, two, or three 5-grain tablets of thyroid substance in a day; or, if it is preferred, a liquid preparation may be prescribed, such as Elixir Colloid (Squire) or the Liquor Thyroidei (B.P.). The dose of Elixir Colloid is from 1 to 2 drachms, but even smaller quantities may be given (1 drachm represents 1½ grains of the dry extract); while the Liquor Thyroidei is given in doses ranging from 5 to 15 drops. Needless to say, these doses must be given entirely according to the individual case, as under no circumstances should thyroid medication be undertaken by rule of thumb. Each case must be treated on its individual characteristics, the length of time during which the disease has been manifest, the degree of thyroid deficiency, and the alterations in the patient which this has produced.

Kendall, of the Mayo Foundation, Rochester, Minn., has isolated a crystalline substance from the thyroid gland containing 60 per cent. of iodine. This he designates alpha-iodine compound. The results following the treatment of myxœdema by this preparation are reported to be extraordinarily good.

When we come to the treatment of the lesser degrees we cannot speak so definitely. The initial dose should always, as we have already indicated, be small. The drug should be increased after some days or weeks, and it should be regarded as a failure of technique if the prescriber ever has to reduce the dose owing to commencing with too large a quantity. He should, so to speak, feel his way, looking carefully for the changes which will show that the drug is doing its work. The temperature will approximate to normal almost from the first, certainly as the circulation feels the result of the additional thyroid extract. The pulse will increase in rate, and, if charted, will show a steady approximation to the normal. It must be remembered that these patients are often small, and that small people have, under normal conditions, a more rapid pulse than large individuals. When we find, therefore, that a small patient has a slow pulse, we should seek for the reason. Again, the subjective symptoms will improve under thyroid medication; the feelings of languor, the extreme chilliness, the depression, and the general discomfort, will diminish in severity.

Provided that such changes are looked for and noted as they appear, it will be safe to increase the dose should they be delayed or incomplete. The administration of thyroid is both an art and a science: an art, because of the skill required to apply correctly the knowledge gained of thyroid-therapy; and a science, because of the exactitude of such application, which is essential if we wish to achieve the best results.

In cases of submyxœdema, it is far better to err on the side of caution—*i.e.*, of too small doses—than of rashness. The former can be remedied as the reaction of the patient indicates; while the latter may not only lose the faith of the patient in this remedy (which is, if the diagnosis be correct, the only remedy), but may even make the prescriber doubt his own judgment. One-tenth to one-quarter of a grain should form an initial dose, certainly in the majority of cases, which, when all is said and done, are in the main minor degrees of deficiency. This may be given two or three times a day, and increased to ½ grain, 1 grain, or even 2 grains, three times a day. Generally speaking, this is quite a sufficiently large dose. There are cases of submyxœdema which require larger doses, but they should only attain to these after a long administration.

One other word of warning, and we may conclude. The prescriber must be able to rely upon his preparation. He must know that the percentage composition is constant, that it contains a due proportion of iodine, and that it is fresh and has not reposed on a shelf in a local chemist's shop for many moons. Thyroid extract degenerates, and when this happens it becomes inert; and it does not take long for this to happen. If the patient fails to react, we must remember that the quality of the drug may be at fault, and not the diagnosis. So long as the drug is fresh, it matters little whether it be given in the form of dry extract, liquid extract, or one of the many prettier preparations on the market. The prescriber must know what he is prescribing, or he will be unable properly to check progress.

Finally, as the treatment proceeds, a careful watch must be kept upon the temperature, pulse, and weight, for mainly on these points can the supply of thyroid extract be regulated.

REFERENCES.

[1] Chapter XIII., p. 192.

[2] *Practitioner*, vol. xciv., No. 1, p. 30.

[3] The Newer Physiology in Surgical and General Practice, by Rendle Short, p. 85.

[4] *Practitioner*, vol. xciv., No. 1, pp. 40, 41.

[5] Hertoghe quotes Murray in saying that these patients show a marked disinclination to discuss these symptoms, and asks whether this is due to the fact that such hallucinations show a marked resemblance to those associated with alcoholism. They are due, Hertoghe believes, to infiltration of the nervous centres, or to more local infiltration, such as thickening of the aural mucosa, Eustachian tubes, and the naso-pharynx.

[6] In myxœdema Brun and Mott have shown the presence of subacute general chromatolysis of nerve cells.

[7] Chronic Intestinal Stasis.

CHAPTER VI

THE PITUITARY BODY

THE existence of this body has been known for centuries, but until recently it has been regarded as of no functional importance—as a vestigial relic. Now, however, the very reverse has been shown to be the case, and since 1895 it has been known that this small gland exerts an active influence upon the general bodily metabolism. Its intimate functions are still far from clear, and experiments have not infrequently led to contrary results. However, the light is beginning to dawn, and clinicians are now reaping the benefits which laboratory workers have made possible by their investigations of the structure and functions of this gland.

These investigations have been made largely with a view to ascertain the results of extirpation experiments, and the conclusion arrived at is this, that, far from being a vestigial remnant and unnecessary to life, its influence upon the health is of prime importance, and that its normal functioning is essential to health.

Its full relation to bodily efficiency has still to be explained, as there are aspects and features about which we should like more enlightenment. The French were wont to refer to the pituitary as "l'organ énigmatique," and its mysteries more than justify such a name. The ancients, while cognizant of its existence, regarded it from a different standpoint. Thus, Galen and Vesalius believed that it was concerned in the formation of the nasal secretion; hence the name "pituitary." Vieussens and Sylvius considered that it was concerned with the manufacture of the cerebro-spinal fluid. The first hint as to its real functions—namely, the manufacture of an internal secretion—is conveyed in a paper to which Cushing calls attention. This was written by Lower, and was called "Dissertatio de Origine Catarrhi," 1672, and contained the statement: "For whatever serum is separated into the ventricles of the brain and tissues out of them through the infundibulum to the glandula pituitaria distills not upon the palate, but is poured again into the blood and mixed with it." Here, then, we have the precursor of our knowledge of an internal secretory organ.

Structure of the Pituitary Body.

The pituitary body consists of three parts: an anterior part (glandular), an intermediate portion, and a posterior or nervous part. The anterior part is composed of a network of epithelial cells, between which run many wide bloodvessels with thin walls. This part of the gland is derived from the buccal invagination (that portion known as "Rathke's pouch "). As Swale Vincent points out, the structure is similar to the adrenal cortex, the islets of Langerhans, the thyroid, the thymus (in its epithelial stage), and the interstitial tissue of the ovary and testis.[1] Next to this anterior part comes the pars intermedia, which, while it is derived from Rathke's pouch, and resembles the pars glandularis in structure, differs from it in that "its cells are less glandular and its bloodvessels much less numerous."[2] This portion of the gland is separated from the pars anterior by a well-defined cleft; but it is not always markedly separate from the pars posterior. This latter portion of the gland is derived from the infundibulum, or stalk of the pituitary. This is attached by its terminal portion to the floor of the third ventricle; while its other extremity expands and forms the posterior part of the pituitary body. This is known as the pars nervosa, and consists of neuroglial fibres and cells.

Histologically the anterior part of the gland consists, as already stated, of " trabecular masses of epithelium-like cells between which are very numerous sinus-like blood-capillaries lying in intimate relation to the cells, which are, indeed, sometimes set closely round the blood-spaces."[3] This is the largest part of the gland, and likewise the most freely supplied with blood. It is supplied " by eighteen to twenty small arterioles which converge towards the infundibulum from the circle of Willis and pass into it along the stalk " (Dandy and Goetsch).[4] This part of the gland, therefore, is one of the most vascular parts of the body.

There are two varieties of cells in this part of the pituitary: clear, non-staining, and granular, staining cells, the latter being divided into oxyphil and basophil. In some animals all the cells are set like a columnar epithelium round blood-sinuses (Schäfer). It is interesting to note that in pregnancy large granular cells are present in unusual numbers, and have been called *pregnancy cells.*

The *pars intermedia* resembles the pars anterior in general formation, but its cells are less granular and it is not so vascular. There is no sharp line of demarcation between the pars anterior and the pars intermedia, but they are distinguished by the character of the cells. Behind the interglandular cleft "the pars intermedia forms a well-marked layer of varying depth; it also extends as a thin stratum over the surface of the pars nervosa, as well as over the neck of the gland which connects the pars nervosa with the infundibulum."*

But the pars intermedia is not everywhere sharply marked off from the pars nervosa, for strands of cells may extend a variable distance between the fibres of the pars nervosa. The granular and hyaline globules, which are present in this part of the pituitary, pass into the pars nervosa and can be traced as far as the "continuation of the third ventricle into the stalk." Herring concludes that the hyaline and granular substances produced by breaking down of the cells of the pars intermedia form a secretion which finds its way into the cerebro-spinal fluid. There seems little doubt,

* Schäfer, "The Endocrine Organs," p. 80.

however, that the pars anterior forms a substance which has a marked action on metabolism, but so far no active principle has been isolated from this part of the gland. The physiological effects of extracts of the posterior lobe are, as we have seen, definite and striking.

The *pars posterior* or *pars nervosa* is formed almost entirely of neuroglial fibres, with neuroglial cells scattered between the fibres. Between these fibres is found a hyaline matter, which is more abundant in the neighbourhood of the stalk. Schäfer maintains that there can be little doubt that the activity of extracts of this part of the gland is due to this substance. Herring denies that any nerve cells are present in the pars posterior, and there are very few nerve fibres.

Physiological Functions.

In studying the physiological action of extracts of the pituitary, we are faced with certain apparent contradictions. If an extract of the whole gland be injected, there is an immediate rise of blood-pressure, associated with a slowing of the heart's action. In this connection the effect of pituitary is similar to that produced by adrenin. The arterial system is affected by this extract, as is all the involuntary tissue of the body—in other words, vaso-constriction is increased; and it is this property which makes pituitary extract such a valuable remedy in shock. We shall refer to this factor when discussing the therapeutic aspect of extracts of the pituitary body.

Certain observers believe that the substance which exerts this tonic action exists in the posterior part of the gland only[5] (which includes in this connection the *pars intermedia* as well as the *pars nervosa*), and, in point of fact, it has been shown that this effect is produced by either the pars intermedia or the pars posterior, but more by the latter than by the former.

As well as this tonic effect upon the heart and the bloodvessels (which, while it resembles that produced by adrenin, differs from it in that this latter extract causes increase in the rapidity of the heart's beat, whereas pituitary extract causes slowing of the pulse), pituitary extract acts upon other plain muscle, such as the stomach, the intestines, the uterus, and the bladder.

As opposed to this general stimulation, there are one or two notable exceptions. The kidney, when stimulated by the administration of extract of the pituitary, reacts in a different manner. Thus, the renal arteries dilate, there is diuresis, and this is partly due "to a selective influence of one of the contained hormones upon the cells of the renal tubules. . . . This action has been supposed to be due to a special diuretic hormone from the pars intermedia, and it is not as yet certain that this is not the case; but it seems more probable that all the effects that it causes are due to the active principles of the posterior lobe."[6]

Again, the effects produced upon lactation by injections of this gland are interesting. Ott and

Scott, in 1910-11, pointed out that it possessed a marked galactagogue action, and since that time many observers have supported this statement. There have, however, been a few dissentients, who maintain that extracts of pituitary have no such effect; these are, however, in the minority.*

Weed and Cushing have shown that extracts of the pars posterior produce a stimulation of the flow of cerebro-spinal fluid, which appears not to be dependent upon a rise of blood-pressure.

One other feature, which at first sight appears rather contradictory, is the effect of pituitary extract upon amenorrhœa. It has been on several occasions utilized to counteract cessation of menstruation, and with marked success. This is, of course, contrary to what we should expect, but can only be explained, as suggested by Harrower, on the assumption that the gland is acting vicariously in carrying on this function. It is known that the pituitary undergoes hypoplasia during pregnancy, and Fromme tried injecting an extract of the gland in amenorrhœa, with some degree of success.

Now as regards the active principles of the pituitary. First of all in importance, certainly from the therapeutic standpoint, is the fact that the majority of observers are agreed that the posterior part of the

* Schäfer maintains that the effect of pituitary extract upon lactation is one of the most striking experiments in physiology; but Heaney does not believe in the galactogogic effect of pituitary extract (quoted in Harrower's "Practical Hormone-Therapy").

gland contains the active principle. Therapeutically, better and more constant results have been obtained by the use of some preparation of this part of the gland than by the exhibition of extracts of the whole gland or by the attempted isolation of extracts of the other portions; although, as we shall see, extracts of the anterior lobe have their therapeutic uses. Harrower states that a definite salt has been isolated from the pituitary—*hypophysin sulphate*—which is available for use, and standardized in 1 in 1,000 solutions. This has been utilized by many observers, who report favourably on its use (Hertzberg, Fuhner, and Harrower).

The Effects Produced by Disease of the Pituitary Body.

In discussing the thyroid gland, we saw that morbid conditions due to its faulty functioning might be classified into those due to hypersecretion (hyperthyroidism), and those due to deficient secretion (hypothyroidism). In like manner, when discussing diseases due to abnormal working of the hypophysis cerebri, we may adopt this division—namely, diseases due to excessive action of the pituitary and those due to deficiency.

The best recognized disease associated with this gland is that to which Marie gave the name "acromegaly" (ἄκρον=point; μέγας=large). It is now believed that this condition owes its origin to a hypersecretion of the pituitary, and that part of the symptoms are directly due to an excess of the hormone elaborated by the anterior part of this gland.* It is also now generally believed that a common sequence in the production of this disease is a primary hyper-pituitarism, the cause of which may or may not be clear, followed in some cases by a hypopituitarism.

Before proceeding to outline the features of these two clinical conditions, we will briefly describe the symptoms of acromegaly. This disease usually commences with a marked narrowing of the field of vision, so that ocular symptoms are a prominent part of the complaint in its early stages. This feature may be due to the presence of a tumour in the gland pressing upon the region of the optic chiasma. Sooner or later are developed the characteristic features of the complaint which caused Marie to describe it under the name "acromegaly." These consist in a marked overgrowth of the head and extremities. The face enlarges and coarsens in its expression; while the shape of the head tends to alter, becoming flatter and squarer. The fingers, if viewed by the X-rays, show an enlargement of the bones, with a "mushrooming" of the terminal phalanges. The entire skeleton increases in size, so that the individual becomes more or less generally enlarged.

Certain other changes are common, and these de-

* Schäfer says: "That the acromegalic skeletal growth is produced by hypertrophy and over-secretion of the anterior lobe is highly probable, both as the result of partial extirpations in animals and from the effect of operative removal of pituitary tumours in man" ("The Endocrine Glands," p. 113).

velope concurrently with the skeletal enlargement. There is a tendency to hypertrichosis, with a general increase of the hair all over the body. Sexual activity diminishes, as a rule, early in the course of the disease: although, in those cases where hyperpituitarism is succeeded by hypopituitarism, sexual activity may be primarily increased, and subsequently diminished. A tendency to glycosuria is common, which, again, may be followed by a diminished glycogenesis. The integument is also thickened, in a somewhat similar manner to that seen in myxœdema; while if the disease commences before ossification of the epiphyses has taken place, the stature becomes enormous and the individual turns into a giant.

It is now generally believed that acromegaly is due to an overgrowth of the pituitary; indeed, in many cases actual tumours are present, and have been demonstrated post mortem. Sometimes, in these cases, the *sella turcica* can be shown by a skiagram to be definitely enlarged. On the other hand, after the glandular enlargement, a secondary atrophy may ensue, in which case the symptoms become those of hypopituitarism. It is at this stage that symptoms contradicting the earlier clinical picture may make their appearance, so that, whereas at first there may have been a tendency to undue glycogenesis, there is now increased sugar storage, and whereas at first there had been hypertrichosis, there is now a change in the hair, the distribution often tending towards the feminine type.

Again, it does not follow that every case of what Cushing calls dyspituitarism may commence as a hyperpituitarism, and subsequently change to a hypopituitarism; for some cases evidence symptoms pointing to the latter condition from the first. The state described by Frohlich, and named by Bartels "*Dystrophia adiposogenitalis,*" is essentially a typical example of hypopituitarism. The symptoms pointing to this state are, as is to be expected, the opposite of those typical of hyperpituitarism. Thus, the stature is small (if the disease commences before adolescence), adiposity is excessive, sexual development is delayed or deficient, the development of hair is wanting, and there is a tendency to the formation of feministic characteristics. Thus, the hair on the pubes is more localized than is the case in man, but the development of the hair on the head is frequently abundant. The sweat is usually deficient, although the skin exhibits a smooth and even texture.

Cushing deals very fully with the production of this state in his book, "The Pituitary Body and its Disorders." He believes that the tendency to the deposition of fat, which subjects of hypopituitarism show, owes its origin to deficiency of the secretion from the posterior lobe. Likewise the unusually high tolerance for sugar and the increased assimilation of carbohydrates are due to the same cause.

Again, in hypopituitarism there are other changes which may be expected in the symptoms. The temperature is usually subnormal, the pulse slow, the blood-pressure low, and the mental attitude sluggish, with a tendency to somnolence. It will be seen that the clinical picture is not unlike that seen in myxœdema. The parallel is, in fact, a close one, certainly in many features.

McKennan, in speaking of epilepsy, states that, from the study of radiograms and from the evidence of the post-mortem room, the pituitary gland is often found to be at fault in this disorder. He believes that pituitary administration should go hand-in-hand with the prescription of the bromides, the latter being gradually reduced in dosage, but the patient maintaining the pituitary treatment for a lengthy period.

It is important to remember that the symptoms of hypopituitarism will differ according to whether the deficiency first appears before adolescence, or is only in action after adult life has commenced. Once the ossification of the epiphyses has taken place, there is no possibility of further increase of stature. But the increase in the integuments, the alteration in the circulation, the changes in the mental outlook—these all point to the underlying cause. Schäfer says that the symptoms differ widely, according to whether the anterior or posterior lobe of the gland is mainly affected; if the lesion is concerned with the anterior part of the pituitary, the chief effects will be upon the stature, while affections of the posterior lobe produce fat formation and deficient sexual development. A deficiency of the pituitary secretion, appearing during childhood, would produce a dwarfed stature,* marked adiposity, delayed sexual development, with absence of the secondary sexual characteristics. The pubic hair, in the male, is confined to the pubic region, and does not extend towards the umbilicus, while there are other signs of feminism present. The extremities tend to be more rounded, there is some degree of genu valgum, a broad pelvis, and sometimes a well-marked mammary development. The skin is smooth and the nails are small and do not show the usual crescents at their bases. It is possible that with one part of the gland functioning adequately, and the other deficient, the clinical picture might correspond to what is expected when the particular part is abnormal. Supposing the anterior part of the gland to be normal and the posterior deficient, we should expect a fully-grown individual, but with excessive deposits of fat, slow circulation, sluggish mentality, and the other features of hypopituitarism, with the exception of stunted skeletal development.

Although much of this particular study leads us into realms of speculation, nevertheless there is strong probability that these suppositions are near the truth. Although the pituitary is by no means always atrophied in dwarfs, this is not tantamount to saying that its secretion is normal qualitatively as well as quantitatively; for it might be enlarged by tumour formation, or by hypertrophy, without secreting the normal amount.

* Cases have been recorded in which the pituitary gland has been found atrophied in dwarfs, although this is not invariable.

Here we must leave the discussion of abnormalities in the pituitary secretion, and discuss briefly the treatment of such disorders.

Treatment of Pituitary Disorders.

In a brief review of the treatment of pituitary disorders, or, rather, of such disorders as come within the scope of this chapter, we must perforce spend some time on the study of both surgical and medical treatment. For, as regards that class of disorder which is caused by a radical change in the structure of the gland or by a tumour interfering with the adequate functioning of the gland either by direct pressure, or by raising the intracranial tension, surgery is not always even a matter of choice, but a matter of necessity.

As we have already said, some cases of acromegaly have shown the existence of tumours of the pituitary gland which have upset its normal secretion. Thus, a cystic growth of the gland, when removed, may produce hypopituitarism, which, again, can be remedied in some cases by pituitary feeding. But previous to the operative measures the symptoms have naturally been those of excessive secretion, sometimes accompanied by localizing symptoms due to an increase of intracranial tension.

Cushing has reviewed the treatment of pituitary disorders very fully in his book,[7] and he deals with the question of surgical interference and with the choice of treatment in a thorough manner. Apart from those cases which show the presence of a tumour, where surgical treatment is generally the only hope at the present state of our knowledge—*i.e.*, with the uncertainty of the minutiæ of the diagnosis—we can scarcely recommend surgical interference for hyperpituitarism, on the same grounds on which some authorities recommend partial removal of the thyroid gland for hyperthyroidism. In this connection Cushing says:

"In view of the fact, therefore, that hyperpituitarism, so far as glandular secretion is concerned, is a condition which tends to right itself, it must remain for the time being a matter of uncertainty as to whether or not, in the absence of a degree of hyperplasia sufficient to cause neighbourhood symptoms, operative measures can hold out any promise of permanently controlling the disorder.

"When, however, neighbourhood symptoms have arisen owing to the extreme enlargement of the gland, due to the formation of an adenomatous struma, whether or not there have been antecedent symptoms of acromegaly, the surgical aspects of the matter stand on firmer ground."[8]

Owing to the situation of the pituitary gland, and the difficulty of operation, we see, therefore, that its partial removal, in the absence of urgent symptoms, is not to be considered, even as a possibility, in the hope of benefiting symptoms of hyperpituitarism. Fortunately, there seems to be a good deal of evidence to point to the assumption that states of hypersecretion are often transitory, so that we must treat the early stages of such a condition with care and watchfulness. It is opposed to our present knowledge to administer extract of the pituitary gland to patients suffering from acromegaly; for as thyroid extract makes patients suffering from Graves' disease worse, so does pituitary extract affect acromegalics.[9] The subsequent hypopituitarism may well be met by organo-therapy; sometimes, indeed, one feels tempted to employ the extracts of other of the endocrine glands in the treatment of hyperpituitarism, in the hope that the hormone balance will be restored. In the present state of our knowledge, however, this latter form of therapy for this disorder must needs be empirical; nevertheless, much has in the past been achieved by empiricism, and doubtless in the future much more will have to be placed to its credit.

Turning now to the study of the treatment of hypopituitarism, we find that medicine naturally takes a more prominent place than surgery. The administration of pituitary substance may be carried out in three ways—namely, by ingestion, by injection, or by grafting. For simplicity of administration, the first is undoubtedly the method of choice, and consequently is the one mainly relied upon in actual practice. From the experimental standpoint, Goetsch found that the subcutaneous injection of the extract in dogs was more effective in the ratio of 4 to 1 than the oral administration, while the intravenous injection was even more effective than the subcutaneous in the ratio of 2 to 1.

These tests were made with the standard devised by Cushing, from whose book they are quoted. This standard is based upon the increased tolerance for sugar which patients suffering from hypopituitarism exhibit; for in hypopituitarism "the rational dosage of glandular extract to be administered by mouth can possibly be determined by giving the individual daily an amount of glucose or lævulose sufficient to produce a temporary mellituria in a normal individual of equal bodily weight; meanwhile an increasing amount of the extract is administered daily, until, under the conditions of increased carbohydrate tolerance which the patient exhibits, hyperglycæmia occurs, with a trace of sugar in the urine."[10]

Having arrived, then, at the diagnosis of hypopituitarism, we next have to decide upon the treatment, both as to the method to adopt and as to the particular preparation to employ. We are concerned here more with the routine administration of pituitary extract (in one of its many forms) than we are with its employment in urgent conditions, such as shock, obstetrical emergencies, etc.; so that this account must be understood to deal chiefly with the treatment of definite hypopituitarism.

Two cases in which preparations manufactured from the anterior lobe were employed with marked success have been reported by Magnier.* These were cases of mental deficiency; in one instance delayed, in the other, arrested mental development.

* *Medical Press and Circular*, September 22, 1920, p. 226.

The first patient was a child, eight years of age, who came under treatment for mental backwardness. There was obstinate constipation present. He was treated with one 2½-grain tablet daily of anterior lobe pituitary gland. From the first he improved markedly, the intellect became much brighter, he could talk and write, and the bowels became regular. The author considers that the natural course of development was delayed by an attack of convulsions as a child.

The second patient was an infant, who, at the age of eighteen months, had hardly developed since his birth. He was unable to sit up, took no notice of outside things, and had an idiotic look. The same treatment was prescribed, and after one month improvement was noted. The child could sit up, made attempts to crawl, and was taking food well, whereas previously he was unable to take any food except fluid.

Both these patients were treated by anterior lobe pituitary gland tablets (Parke, Davis and Co.), and the results are certainly suggestive of the help which can be gained by pituitary extract in cases of delayed development.

An interesting note by Davidson upon the value of injections of pituitrin is to be found in the *British Medical Journal* of August 21, 1920.* The patient, an ex-soldier, was admitted to hospital "with a history of bronchitis and nephritis (*sic*)," contracted on the

* "The Antidiuretic Effect of Pituitary Extract in Diabetes Insipidus."

Salonica Front. On his way to England he noticed polyuria for the first time. In hospital, in England, he was passing just over 300 ozs. of urine in the twenty-four hours. Injections of pituitrin were given, and these produced a marked fall in the amount of urine passed. Pituitary extract by the mouth, however, had no such action.

This case is quoted as it is an example of the relative merits of hypodermic administration and injections. When we wish to get a specific effect upon a disorder such as diabetes insipidus, the hypodermic or intramuscular route is preferable.

If it is decided that pituitary extract is required over a lengthy period, it is far preferable to administer it by the mouth, as there are many disadvantages attached to both the other methods. Where it has to be given repeatedly by injection, the intramuscular method is the one for choice, as subcutaneous injection is undesirable on account of the local anæmia produced. For a very rapid result, it may be administered by intravenous injection well diluted with normal saline solution.

As to the various preparations which are on the market, a wide selection is before the prescriber. *Pituitrin* may be administered by hypodermic or intramuscular injection, or by the mouth. The dose in the latter method is from 10 to 30 minims.

This preparation is said to be especially cardio-tonic in action, "and in a less degree hypertensive."[11] Again, Hypophysin (Fuhner) is stated to possess, from the physiological standpoint, "the essential properties of the extract of the macerated posterior lobe."[12] These and other liquid preparations are usually put up in ampoules, should it be desired to administer them hypodermically or intramuscularly. The dose of the liquid preparations is usually from 8 to 16 minims. A preparation which will be found useful in practice is the Elixir Hypophysis (Squire), which is manufactured from the whole gland, 1 teaspoonful representing $\frac{1}{2}$ grain of the dried and powdered extract. The dose is from 1 to 2 drachms two or three times daily.

Again, pituitary extract is manufactured in solid form, either as a separate preparation or in combination with other of the endocrine gland extracts. These products are very numerous, and it would be tedious to mention them in detail; suffice it to say that most of the wholesale chemists manufacture such extracts in tablet or powder form.

It is, of course, as important in dealing with this extract as it is in dealing with thyroid extract that there should be a known standard of strength, and that the prescriber should be sure that his preparation is fresh. As a rule this is easily ascertained, and the dosage regulated with some degree of certainty.

Many manufacturers place on the market preparations specified as having been made from the anterior or posterior part solely, and thus another variety of this treatment is introduced. The majority of cases appear to indicate treatment with posterior extract; indeed, the majority of the preparations are expressly stated to have been manufactured from the pars posterior.

Now as to small points in the treatment of pituitary disorders, and also in the utilization of this extract in counteracting symptoms. First in importance is undoubtedly its contra-indication. As pituitary extract raises the arterial tension, it (or any preparation containing it) should be carefully avoided in all states indicating hypertension. It should be administered with caution over long periods, and frequent sphygmomanometric readings taken to control any undue rise in blood-pressure. The present writer has known it work wonders in some neurasthenic conditions, likewise in states of weakness following long-continued strain, in impotence and such disorders. Again, in delayed convalescence, in persistent low blood-pressure, in depressive states, and the like, a course of pituitary extract, wisely controlled, will frequently be found to be invaluable.

The requisite dose varies enormously, and so wide is the range that it appears probable that some at least of the failures are due to the dose being unsuitable. In speaking of the dosage required in some of these cases, Cushing emphasizes the vast range of dose which is effectual in different cases. Thus, one boy exhibiting the signs of hypopituitarism in a marked manner underwent a "complete mental, moral, and physical awakening" by taking 18 grains of whole gland preparation daily. But another case quoted by the same author required as much as 300 grains daily (a prohibitive dose, as Cushing remarks) to give the same subjective benefits which other patients experienced with far smaller doses.

In undertaking the treatment of a patient by means of pituitary extract, it is wise to progress slowly, and to endeavour to ascertain the dosage required by the individual case, as well as the reaction to the extract. In practice, it is often necessary to rest content with methods which are, perhaps, not so precise as those which are open to laboratory workers; and it is therefore often only possible to watch carefully the progress made under the treatment, at the same time looking for any symptoms the amelioration of which may justifiably be claimed to be due to the drug.

Cases are sometimes encountered, however, especially in neurasthenic subjects, in which irritability is produced by the administration of pituitary extract. Often this appears to be due to the rise in blood-pressure which follows such treatment; but it is well to be careful to reduce the dose should this symptom appear, or even to cease its administration altogether, and after a few days' cessation to recommence the treatment with small doses. This will generally be successful in combating the irritability, and will enable the treatment to be persevered with after the rest.

In Chapter XIII. the use of pituitary extract in combination with other organic extracts is fully discussed, also the joint administration of this substance and thyroid extract is considered.

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[2] Schäfer, The Endocrine Glands, p. 77.
[3] *Ibid.*
[4] Quoted by Schäfer, The Endocrine Organs, p. 78.
[5] Howell, *Jour. Exper. Med.*, 1898, iii. 245-258.
[6] Harrower, Practical Hormone-Therapy, p. 305.
[7] H. Cushing, p. 294 *et seq.*
[8] *Ibid.*
[9] Experiments of Renon and Delile, quoted by Cushing, p. 315.
[10] Cushing, pp. 317, 318.
[11] Harrower, p. 313.
[12] *Ibid.*

CHAPTER VII

THE ADRENAL GLANDS

THE study of the chromaffin system involves a careful investigation of its most important member—namely, the adrenal or suprarenal glands. These bodies are now known to possess such vital properties in the body physiology, and to perform such an indispensable part in the maintenance of the "tonic" state of all vascular and plain muscular structures, that they deserve a foremost place in any study of the endocrine glands.

Although as long ago as the sixteenth century the great anatomist Eustachius discovered the existence of the adrenal bodies, their importance remained unknown until recent years. In 1849 Addison discovered that, in some cases of illness characterized by definite pigmentation of the skin, the adrenal glands were found to be diseased, often with a tuberculous infection. From that day to almost fifty years after, our knowledge of these structures may be said to have increased but little; but in 1894 the famous discovery by Oliver and Schäfer, that extracts of the glands possessed a marked blood-pressure-raising property, inaugurated the interest which has led to the really remarkable discoveries of the properties which the chromaffin system in general, and the adrenals in particular, possess.

Before commencing the study of the therapeutic value of extracts of the adrenals, we must briefly outline our knowledge of these glands, both from the anatomical and physiological standpoint.

Anatomy and Physiology of the Adrenal Glands.

The suprarenal glands are two flattened bodies more or less globular in shape, of a yellowish colour, and are situated behind the peritoneum in front of the upper part of each kidney. Their size in normal health varies in different individuals, but as a rule the left is slightly larger than the right, and situated somewhat higher up. The former is semilunar in shape, while the latter is more triangular, and somewhat resembles a "cocked hat."

In structure these glands are made up of a central portion, or medulla, and a peripheral part, or cortex. The former is composed of highly vascular cells, embedded in a venous plexus, which secrete adrenalin; owing to this property they stain more or less deeply with chromate salts, which has earned for them the name of "chromaffin cells." According to the depth of stain which the cells of the medulla take, the degree of activity of their secretion can be roughly estimated.

The medulla of the suprarenal gland has very close nervous relations, which, from a morphological standpoint, would be expected. For early in embryonic life neuroblastic cells emigrate, and while some settle in front of the spinal cord, forming the ganglia of the sympathetic chain, others eventually become the visceral ganglia; while another group, not converted into nerve ganglia, remain in close connection with the kidney, forming the medullary cells of the adrenals, which secrete its active principle. As well as the medulla, which is formed in this manner, certain clumps of cells stray farther afield, forming accessory bodies external to the main gland.

The importance of these facts is shown by two characteristics of the gland; the first is that it is these cells, originally formed from the same embryological tissue as the great ganglia, which secrete adrenalin; the second is that this secretion stimulates only that plain muscle in the body which is supplied by the sympathetic system. That this is so can be verified by electrical stimulation of the sympathetic nerves, which corresponds exactly with the result of adrenalin stimulation.

The exact composition of adrenalin has been discovered by Takamine, to whom we owe the isolation of this substance; and he shows that it is ortho-dioxy-phenyl-ethanol-methylamine. Its secretion into the blood-stream is controlled by the splanchnic sympathetic nerves. Moreover, the amount of secretion has been shown to depend largely on other factors, both mental and physical. Thus, mental agitation—fright, emotion, hurried exertion, etc.—all exert an influence upon the secretion of this substance. It is to the cells of the medulla, therefore, that we owe this important hormone—in this case a true hormone, as it is an excito-tonic chemical. These cells, it must be remembered, have an extremely intimate connection with the sympathetic nervous system; this is important, as we shall see when we discuss the effects of hypo-adrenia.

The other part of the gland is of different structure, and is composed of fatty material; a doubly refractive lipoid is found in the cortex, with which this part of the gland is loaded. The cortex is very much larger than the medulla; in fact, it forms about 90 per cent. of the whole gland.

Included in the chromaffin system are the following bodies: the medulla of the suprarenal gland, the carotid gland, and the intercarotid body, the accessory adrenals, and some of the cells of the anterior lobe of the pituitary body which give the same reaction to chromate salts.

While the medulla is in reality a part of the nervous system, at all events morphologically, the cortex is not in any way connected or controlled by the sympathetic nerves. From an embryological standpoint, its cells are derived from the same neighbourhood as the sexual glands, and as the testes or ovaries descend they carry with them processes from the same area. Elliott maintains that there is reason to believe that some buds of this nature are embedded in the sex gland itself, giving rise to the lutein cells of the ovary or the interstitial cells of the testis.[1]

The cortical cells, however, are glandular structures, and appear to supply some secretion which influences the growth and reproductive powers of the individual. This has been demonstrated clinically, for cases are on record where tumours of the adrenal cortex have been found in cases where the characteristics of the opposite sex have developed; in one girl, quoted by Elliott, the menses ceased, a beard commenced to grow, and the body took on masculine characters.

It is stated, also, that enlargement of the adrenal cortex takes place during breeding and pregnancy: and feeding of young animals with adrenal gland substance seems to stimulate the growth of the testes.*

An interesting case, in which an autopsy was performed, has been recorded.† The patient was a woman, age unstated, who was bald, but had a dense beard and moustache. There had been amenorrhœa for three years, and there was pigmentation of the face. At the post-mortem examination, the right adrenal gland was found to be hypertrophied, and weighed 141 grammes.

Effects of Removal of the Adrenals.

Since the time of Brown-Séquard it has been known that removal of the adrenals was followed by death, and that the cause of death was the loss of the internal secretion of these bodies. That death is not due to

* Vincent, S., quoted in *Endocrinology*, October-December, 1917, p. 516.

† *Ibid.*, p. 534.

shock is shown by the fact that the animal shows no symptoms for the first day after the operation, that in many animals life is preserved for several days, and finally, the symptoms which precede death are those now known to be due to loss of the adrenal secretion, and are not those due to shock.

Removal of one capsule appears to have no deleterious effect upon the animal. It lives quite happily until the other adrenal is removed, when death occurs, usually within thirty-six hours (Sajous).

To understand whether the suprarenal capsules are as essential to life in man as in the lower animals it is necessary to consider the effects of a disease which robs the blood of its adrenal content. Many difficulties stand in the way here, for, as Sajous says, the effects of growth of the adrenals are slow in their manifestations; other viscera may be involved and metastatic growths may be present, all of which factors make the clinical study very difficult. The one condition which is able to help us in studying the symptoms of a sudden loss of adrenal secretion is hæmorrhage. Sajous quotes François Arnaud's eighty cases of "suprarenal apoplexy." Briefly, these showed either sudden death or death in a short period, the autopsies revealing hæmorrhagic foci either into both capsules or hæmorrhage into one capsule and congestion of the other. Of seventeen cases of sudden death, fifteen showed "suprarenal apoplexy in both organs, while two showed involvement of one organ. These two instances might invalidate the evidence adduced, could the sudden death in them not be shown to have been due to other causes. But such is the case; in the one . . . the hæmorrhagic adrenal had been ruptured, and the patient died of hæmorrhage into the peritoneal cavity; in the other . . . death had resulted from uræmia, due to granular and cystic degeneration of the kidneys."*

The loss of one adrenal in man produces results analogous to the same condition in animals, as is proved by the operative removal of growths of the suprarenal. We may assume, therefore, that in man, as in animals, the loss of one suprarenal capsule is followed by no bad result, whereas the loss of both is fatal.

Functions of the Adrenal Bodies.

The first point to emphasize in this section is the far-reaching and important part which the internal secretion of the adrenals plays in promoting the bodily harmony. This will be easy to understand when we realize that these glands are essential to life, and that their removal is followed by an early death.

It has been shown that the adrenal secretion, when injected, has a marked effect in raising blood-pressure, and that the injection of blood from the suprarenal vein into a normal animal has a similar effect. Experiments have likewise been performed to show that it is the loss of the blood-pressure-raising substance

* Sajous, "Internal Secretions and Principles of Medicine," vol. i., p. 7.

after removal or disease of the adrenals which is responsible for the symptoms; for the injection of the adrenal blood will remove or modify these symptoms, while this result is obtainable with no other extract—*e.g.*, thyroid, pancreas, kidneys, liver, spleen, etc. We can assume, therefore, that the adrenals secrete into the adrenal veins a substance which is essential to life. This substance is responsible for the maintenance of the blood-pressure and for the stimulation of the cardiac tone. That this latter effect is not due to stimulation of the vagus is shown by experiments, notably of Biedl, who found that injection of suprarenal extract raised the blood-pressure even when the entire spinal cord had been removed. Its action upon the muscular wall of the vascular system—indeed, upon the muscular system in general—is of a constricting or tonic nature. A freshly excised vessel—one, that is, freed from all nervous control—responds to a solution of suprarenal extract (Oliver and Schäfer, quoted by Sajous).

Suprarenal extract has been shown by the same investigators to act directly upon the muscles of the bloodvessels, even after section of the cord.

The absence of muscular tone, and the presence of vaso-dilatation, which is characteristic of hypo-adrenia, may be used as evidence of the functions of the suprarenal glands. The work of the adrenal secretion is concerned, *inter alia*, in the maintenance of the vascular tone, and consequently the blood-pressure. It has a direct action upon the heart itself, and Biedl shows that an injection of suprarenal extract increases both the rapidity and power of the cardiac contractions. The action of adrenalin is "wholly confined to tissues with a sympathetic innervation; and, moreover . . . the effect of adrenalin, in any part of the body, is identical with that produced by electric stimulus of the sympathetic nerve supplying that part. Where the influence of the nerve is stimulating, exciting contraction or promoting secretion, the action of adrenalin will also be stimulating. Where, however, irritation of the nerve is followed by inhibition, the injection of adrenalin will also produce inhibition."* We will now study the chemistry of the adrenal secretion and its effects upon the body.

Adrenalin.

The active principle which is secreted by these glands has been named "adrenalin." It possesses certain very definite characteristics, and is a necessary secretion for the continuance of life, for, as we have seen, loss of both adrenals is fatal, although one adrenal can be removed without any apparent ill effects.

With regard to adrenalin itself, its most striking characteristic is its power of raising blood-pressure, even when injected in small doses. Experimentally, about one-twentieth of a milligramme when injected into an animal is sufficient to cause a considerable rise in the sphygmomanometric reading; which, again,

* Biedl, "The Internal Secretory Organs," p. 189.

is even more noticeable if the vagus is put out of action, as this substance also causes a slowing of the pulse when injected. If this is done, the blood-pressure may rise in quite a remarkable manner. This effect is produced by a vaso-constricting action upon the walls of the peripheral bloodvessels. Oliver and Schäfer showed, by means of oncometric readings, that the volume of the viscera was very markedly reduced by adrenalin, while the volume in the extremities was increased owing to the excess of blood reaching them from the splanchnic area.

Adrenalin, or ortho-dioxyphenyl-ethanol-methyl-amine, is a near relation of tyrosin, or oxyphenyl-amino-propionic acid, one of the products of the decomposition of proteids.

A full account of the chemistry and physiology of adrenalin will be found in Biedl's book on the internal secretory organs, in Swale Vincent's book, and in many other studies of this subject. Sufficient has now been said to show that this secretion is very important in bodily metabolism, and exerts a considerable influence upon the cardio-vascular system. The cortex is supposed to have an internal secretory function, which is concerned in neutralizing the poisonous products of muscular activity. In other words, the medullary secretion exerts an angio-tonic influence, while the cortical is concerned with neutralizing toxins. There seems to be a good deal of evidence that the adrenal secretion is in some way concerned with muscular energy; it is a well-known fact that in Addison's disease, where hypo-adrenia exists, muscular asthenia is a marked symptom; also that muscular power is raised "after adrenal secretion is invoked, or after epinephrin is injected."[2] Where the adrenal glands are injured (which sometimes happens during operative procedures in the neighbourhood of the kidney) or diseased, there can be little doubt that muscular efficiency is diminished. Langlois has shown that the adrenals are concerned in the destruction of muscle poisons.[3] So we are justified in assuming that one function of the secretion of these glands is to keep up cardio-vascular tone, while another is to neutralize poisons elaborated during muscular energy.

It will have been noticed that we have laid stress here upon the intimate relation between the adrenals and the sympathetic system. The present writer has on several occasions laid stress upon the sympathetic symptoms so commonly present in neurasthenia, and has hazarded a theory that in many instances of this condition the underlying cause is sympathetic involvement.[4] The low blood-pressure, the generalized asthenia, the vasomotor symptoms, are, certainly in the majority of cases of true neurasthenia, the most striking features.*

* It has been shown that an intramuscular injection of 1 milligramme of adrenalin caused an increase of secretion of hydrochloric acid in the stomach, and augmentation and acceleration of the contractions of the gastro-intestinal tract.

The fact that neurasthenia is so often associated with gastro-intestinal atony, and the possibility that this is due to hypo-adrenalism is interesting.

Following up this line of argument, we should expect to see much improvement in these patients after the administration of a vaso-tonic hormone, such as adrenalin. And in many cases, in the experience of the writer, this has happened. Doubtless some patients suffer from a combined endocrinous derangement, and these would not of necessity benefit from adrenal administration alone. But, nevertheless, the similarity between hypo-adrenia and neurasthenia is sufficiently striking to be noted.

The features of a disorganization of the adrenal system are daily receiving more attention, and Sargent "has distinguished three different types of adrenal insufficiency—the chronic, the subacute, and the acute."[5] He maintains that many of the manifestations of acute illnesses are due to adrenal insufficiency. It is obvious that such features might conceivably be due to this cause, and when further light has been shed upon the endocrine glands, it is probable that we shall have to revise many of our existing views on the manifestations which accompany febrile disturbances. We shall certainly have a better opportunity of explaining factors hitherto regarded as necessary but inexplicable features of many diseases.

Adrenal Insufficiency.

We have already referred to the views held by Sajous on the adrenal system, and the importance he ascribes to this secretion in the maintenance of efficient oxidation. His views upon adrenal insufficiency, or hypo-adrenia, may be summarized as follows:

" . . . Hypo-adrenia, or insufficiency of the adrenals, means far more than the effects of lowered blood-pressure and the adequate destruction of muscular wastes; *it means, besides, inadequate oxidation and therefore imperfect tissue metabolism and nutrition, and also impairment of the autoprotective functions of the body at large.*"* The three clinical forms of this disorder Sajous describes as *functional hypo-adrenia,* where the adrenals are functioning inadequately, although not the seat of organic disease; *progressive hypo-adrenia,* or *Addison's disease,* where the activity of the adrenals is progressively impaired by organic lesions; and *terminal hypo-adrenia,* occurring as a sequela to infectious diseases and toxæmia.

The symptoms can be studied together. Of prime importance is a low blood-pressure, an asthenic condition of mind and body, a subnormal temperature, a headache of a "vacuum" nature, and the dermographic sign described by Sargent.† The same observer refers to certain complications of convalescence, which he regards as due to a subacute inflammation of the adrenals; while other observers also lay stress upon the exhaustion which may supervene during the course of a fever. This may presumably be due to an exhaustion of the adrenals, produced by their efforts to safe-

* "Internal Secretions and Principles of Medicine," p. 82.

† This consists in a white line which appears on the skin of the abdomen when lightly stroked with the finger.

guard the organism from toxæmia.[6] It is quite possible that these small glands play an important part in all such febrile states, in neutralizing toxins, and in helping to maintain blood-pressure. In any case, it is stated that their administration in such conditions can be relied upon to counteract these effects.

The clinical state of the patient with Addison's disease needs no detailed description here. The flabby atony and muscular weakness, the vasomotor debility, as shown in the coldness of the skin surface, as well as the characteristic pigmentation, are too well known to require minute detailing. As Elliott points out, all the symptoms, except the pigmentation, can be explained by the vasomotor derangement and the paralysis of the sympathetic nerves.[7]

There is also in this disease gastro-intestinal disturbance, as shown by vomiting and diarrhœa; but the danger undoubtedly lies in the risk of heart-failure. Other symptoms are anorexia with deficient appetite, sometimes constipation, attacks of vertigo, syncopal attacks, subnormal temperature, with coldness of the extremities. There are frequently found a persistent thymus, an enlarged spleen, more or less generalized hypertrophy of the lymphoid tissue of the body, particularly of the stomach and intestines. There is usually some degree of wasting; indeed, in the more severe cases a considerable degree of emaciation may be present. These constitute the graver form of the disease. As a rule, although muscular strength is very markedly diminished, general nutrition is not affected.

Death occurs from asthenia, delirium or convulsions, sudden syncope, or, in some cases, generalized miliary tubercle. The main features of Addison's disease are the markedly feeble pulse, the extreme asthenia, the pigmentation, and the gastro-intestinal disturbance.

The milder degrees of hypo-adrenia are those to which we have already referred, and they are frequently labelled "neurasthenia." That is to say, the main features are asthenia, vasomotor disturbances, and a low blood-pressure. In speaking of these forms, Harrower says: "The disorders of the adrenals, accompanied by anatomic changes, are fortunately not very common, while functional hypo-adrenia (sometimes termed 'hypo-epinephrinia'), varying very greatly in degree and the consequent manifestations, is of frequent occurrence. In general, the evidence of the presence of such conditions is lack of vascular tone, hypotension, myasthenia, and instability of the sympathetic nervous system. This class of disorders is still frequently overlooked, and, because of the intimate relations of the endocrinous organs, almost invariably associated with, and complicated by, disturbances in other internal secretory organs."[8]

It might be expected that the extreme weakness and asthenia which are associated with this condition would be accompanied by great bodily wasting. But this is by no means always so; in fact, the bodily weight usually is not lost in any marked degree. It may be that this is due to an increased storage of fat or carbohydrate in the body, due to the diminished glycogenesis; for we know that an injection of adrenalin increases the conversion of glycogen into glucose, and may produce glycosuria; therefore a diminished adrenalin content in the blood-stream might prevent a utilization of the stored-up glycogen, and produce a diminished combustion. This would be probable, seeing that the bodily heat is lowered, with an extreme degree of subjective feelings of chilliness.

Treatment.

Having now very briefly reviewed the symptoms of hypo-adrenia, we will turn to the study of the therapeutics of the adrenals. Opinion is divided as to the beneficial effects which result from the administration of adrenalin to patients suffering from gross deficiency of this hormone—*i.e.*, Addison's disease. Thus, Elliott says: "Neither with animal experiments nor in man has treatment with adrenalin been proved to be of value in prolonging life. I have used hypodermic and intravenous injections of adrenalin without obvious benefit. Still, the substance is worth a trial." On the other hand, Harrower says: "Addison's disease was naturally first among the disorders in which this form of treatment was tried; and while the results have been by no means uniform, numerous cases are recorded by such men as Oliver, Langlois, Osler, Robin, and others, in which the general condition was improved, pigmentation was diminished, and nutrition was benefited. In most cases the results were temporary, though Beclere obtained a complete and permanent cure in one case. He credits the treatment with causing a compensatory hypertrophy of the unaffected areas of adrenal tissue."[9]

Again, it has been suggested that in some cases the causation is solely referable to the adrenal glands, while in others the sympathetic system is at fault, with or without adrenal disturbance; and that in the first class of case benefit is to be expected from adrenal therapy, while in the second we cannot and do not see improvement from the administration of the hormone. As it is generally believed that 80 per cent. of the patients who suffer from this disease are the subjects of tubercle, the general antitubercular treatment should be insisted upon, whatever hormonic treatment they receive. In any case, the dose of adrenal substance would have to be large, and Harrower says that as much as 2 or 3 grains of desiccated gland substance should be given three times a day.

We must believe, therefore, from the summation of evidence, that, so far as is at present known, the administration of adrenalin has not been the success in Addison's disease that it was expected to be. But the explanation probably is that, if the larger part of the gland is destroyed by tubercular or other mischief, the substitution of its secretion is not sufficient, and the disease progresses in intensity; or that the preparation employed is not assimilated in an active form. It has been stated that adrenalin, when given by the mouth, is not destroyed in the stomach nor by the pancreatic secretion, but that the liver acts adversely upon it by depriving it of some of its efficacy. It has been suggested that it is better administered by the rectum, where it can be readily absorbed and carried directly to the vena cava. With regard to the utilization of adrenal extracts for other conditions, it has been tried and recommended for a variety of diseases. Thus, it has been administered as a vaso-tonic in cholera, with, according to the particular author, who believes that this disease is an "acute hypo-adrenia due to poisoning of the adrenals by toxins of the cholera spirillum," immediate and gratifying success.[10]

It has likewise been utilized in the vomiting of pregnancy, in the belief that the adrenals stand between the body and the toxæmias of pregnancy which arise in the chorionic villi. Again, in the condition known as "cyclic vomiting" it has been tried with apparent success.

It will be seen from these quotations that, so far, the diseases mentioned have been acute, and often present no known etiology. It is, therefore, more than possible that the chromaffin system is at fault. But there are encountered other conditions of a more chronic nature which appear to yield to adrenalin, and these are more particularly seen in children. Thus, a boy or girl who developes asthenia, in some cases after an acute specific illness, with languor, hypopiesis, and "backwardness" at school, is possibly suffering from hypo-adrenia. And it has been stated that administration of adrenal extract counteracts this condition, renders the patient more active, and banishes the indolence.

Again, after acute illnesses in adults, where asthenia and delayed convalescence is a marked feature, the exhibition of adrenal extract should deserve consideration. It is not improbable that a disturbance of the adrenal hormone (which, it must be remembered, is a hormone in the real sense of the word) contributes to the slow recuperation and hinders recovery. Therefore, an extract of the adrenals seems to be indicated. Or, alternatively, a pluriglandular preparation should be selected if it is considered, on all the evidence, to be desirable.

Adrenalin, or an adrenal extract, has been tried in exophthalmic goitre, but, so far as the present writer's experience is concerned, the results have not been encouraging, and, in view of the physiological data referred to in Chapter I., this can scarcely be wondered at.

Blair Bell believes that osteomalacia should be treated by means of suprarenal extract—not necessarily because this extract is antagonistic to the ovarian hormone, but because he believes there is often suprarenal inadequacy in this disease.[11] He thinks that the secretions of the adrenals are of value during pregnancy in "assisting the absorption and retention of lime." In this connection it is interesting to note that certain observers have experimented upon the action of adrenalin upon the growth of bone, and have found that animals from whose bones rings of tissue have been removed, if subjected to the ingestion of this extract, heal with bony union much more rapidly than the control animals who are not subjected to the action of this drug. It would seem, therefore, that adrenalin exerts a helpful influence upon the growth of osseous tissue.

Vernet believes that vertigo can be usefully treated by administering adrenal extract. This view is based upon the vasomotor origin of this complaint, and upon the fact that it is commonly seen in chlorotic girls, at the menopause, and in gouty subjects. He gives from five to twenty drops of the 1:1,000 solution twice daily for ten days.

Now as to the methods of administrating the adrenal preparations, and the different varieties which may be utilized. The extract of the gland may be given either separately or in combination with other hormones. Thus, Houssay recommends the combination of adrenalin and hypophysin, and maintains that given together a smaller dose of the former extract is required, which, as it is the more toxic of the two, is a decided advantage. "The combination may be used successfully in fulminating intoxications associated with hypotension, in tachycardia, and in myocarditis toxica, either subcutaneously or by the mouth. The combination produces a greater and more persistent local ischæmia than adrenalin alone. The adrenalin neutralizes the powerful enterokinetic action of hypophysin, while the active constituent of the posterior lobe of the hypophysis counteracts the mydriatic effect of the adrenal extract."[12] Swann has found that moderate doses of a 1 in 1,000 solution of adrenalin administered hypodermically completely cured, in two doses, urticaria.

The extract of this gland may be given either as a liquid preparation or as a solid extract. Adrenalin or adrenalin chloride may be administered by the mouth, hypodermically, or intravenously (the latter in emergencies). The first of these methods is the routine for the majority of cases—*i.e.*, where the treatment is required in small doses, probably over a lengthy period. Again, where it is to be utilized, not because there is definite evidence that the adrenal substance is deficient, but either as a counteraction to other hormones which may be presumed to be in excess or simply for its therapeutic action, this preparation may be relied on. Orally it may be given in doses ranging from 2 to 3 minims up to ½ drachm. The dose hypodermically should be about half—that is to say, up to 15 minims.

This extract has also been used in the treatment of asthma, with a considerable degree of success. It may be given hypodermically or locally as a spray or douche to the nasal mucous membrane.

Preparations of the gland are also made in the form of dry extracts, but the dose appears to vary with different authors. Thus, it is sometimes recommended in doses ranging from ¼ to 3 grains (for mild hypoadrenia), and it is possible that this variance is to be explained by the fact that different authorities are referring to different preparations. Again, some manufacturers supply a tablet containing the extract of several of the ductless glands, such as thyroid, pituitary, and adrenals. If it is desired to give a pluriglandular preparation, such as this, it is important to know the exact dose of each extract which the tablet contains. A more detailed reference to the various preparations will be found in Chapter XIII.

We may mention here a possible method of counteracting hyperadrenia. The patient with over-action of the adrenals is by no means uncommonly met with, but the accurate treatment of such a case is difficult. He is usually thin, nervous, with digestive instability and disturbed sleep. It is always worth while to treat such a patient with pancreatic extracts, as the antagonism between the adrenals and the pancreas is well proven. It may be assumed that such extracts will help to antagonize the excessive secretion from the suprarenal glands, and thus assist in the maintenance of a normal balance.

Finally as to the contra-indications of adrenal therapy. It will be quite obvious, from what has already been said, that hypertension is an absolute contra-indication; also that it should never be administered in diabetes, as it is well known that the output of sugar is increased by the administration of adrenalin. While its value in the treatment of tuberculosis is great, its employment in patients suffering from phthisis should be carefully considered, bearing in mind the possibility of hæmoptysis.

Provided that it is given under the careful observation of a medical man, who can observe the changes which accrue as the treatment progresses, more particularly with regard to the vascular tension and pulse, it is not only a safe remedy, but a particularly successful one. We shall refer in a subsequent chapter to the important points in pluriglandular therapy, and to the factors which decide our choice between the prescription of a single hormone or a preparation containing the extracts of several of the ductless glands.

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CHAPTER VIII

THE PANCREAS

The next gland which we must study in connection with the endocrine glands is the pancreas. And from its importance in the bodily metabolism, an importance which is receiving fresh proofs every day, it deserves a high place in any volume which deals with the internal secretions. Apart from the vital nature of its external secretion—that is to say, its digestive ferments—there is an ever-accumulating mass of evidence to show that the pancreas is concerned with the regulation of carbohydrate metabolism in an even more important relation than are the thyroid and pituitary glands.

For this reason alone, therefore, it behoves us to have a practical knowledge of the pancreas and its functions, and to familiarize ourselves with the results of recent physiological research. We shall therefore devote this chapter to a consideration of the structure, functions, and pathology of disorders, of this gland, and conclude by outlining the therapeutic possibilities.

Anatomy and Physiology of the Pancreas.

The pancreas is a tubulo-racemose gland, situated transversely across the posterior wall of the abdomen, at the back part of the epigastric and left hypochondriac regions. In structure it resembles the salivary glands, although it is of softer consistency and less compact than these organs. It is composed of a head, a neck, a body, and a tail; while its duct has received the name of "the canal of Wirsung." This duct opens into the duodenum, either in common with the ductus communis choledochus or else by an independent orifice.

The gland is composed of alveoli, loosely held together by connective tissue, containing in its meshes cells known as the "islets of Langerhans." These cells are of great importance, for, as we shall see later, they are concerned, as physiological research has shown, in the production of a hormone which governs carbohydrate metabolism. They are plentifully supplied with bloodvessels, arranged in the form of a compact network of capillary vessels.

For many years these cells have been known to exist, but until recently their function has been hidden. Now, however, it is becoming increasingly clear that they, in all probability, secrete a hormone which is absolutely necessary for the continuance of life. Previous to the recent work on internal secretion, the rôle played by the pancreas was supposed to be solely one of digestion; but Bayliss and Starling showed as long ago as 1902 that the digestive juices of the pancreas were capable of being stimulated by a substance known as secretin, which is derived from pro-secretin by treatment with an acid. In normal digestion, pro-secretin, when it comes into contact with the acid of the gastric juices, is converted into secretin, which sets up pancreatic activity.

The external secretion of the pancreas is composed (according to Halliburton) of water, organic solids, and inorganic salts. The organic solids consist of the ferments trypsin, amylopsin, steapsin, and a milk-curdling ferment, together with other less important constituents, such as traces of leucine, tyrosine, and a small amount of proteid matter.[1]

These ferments are most important in carrying on the digestive processes inaugurated in the mouth and stomach; but as their chemical actions are physiological facts not directly connected with our study, we will not deal at any length with them here. What does concern us in this connection is the internal secretion of the pancreas, and the influence it exerts upon metabolism in general.

As we have already said, the islets of Langerhans are of great interest in studying the internal secretion of this gland, as recent work has confirmed the theory that it is this part of the pancreas which is so essential to life.

The Internal Secretion of the Pancreas.

In 1889, V. Mering and Minkowski made the important discovery that removal of the whole or of a large part of the pancreas was followed by hyperglycæmia, and eventually fatal diabetes. That this is not due to the abolition of the external secretion is proved by the discovery that, if pancreatic substance is grafted into an animal, glycosuria is prevented, although the secretion of ferments into the alimentary canal is absent. Again, if the pancreatic duct be tied, the pancreatic tissue atrophies, but it is believed that the islets of Langerhans remain in a sufficiently normal condition to furnish the body with the internal secretion. For although diabetic symptoms do not ensue after ligature of the duct (in spite of the atrophy of the pancreas), if the organ be subsequently removed glycosuria results.

Again, in support of the belief that the islets are responsible for an internal secretion, it has been noted that these cells are degenerated in some cases of diabetes, which is strong presumptive evidence that pancreatic diabetes owes its origin to an interference with an internal secretion provided normally by the cells in the islets of Langerhans. Schäfer says that these cells have a common origin with the cells of the duct, although they are not connected with the alveoli or ducts.[2]

Without going into elaborate details of pancreatic physiology, we must give the bare outline of the structure and behaviour of this gland, in order that its bearing on the hormone balance and its relation to carbohydrate metabolism may be clear.

To summarize the modern view as to the relationship which the pancreas bears to diabetes, we may say that it may fairly be assumed that the islets of Langerhans secrete a substance which, circulating in the blood-stream, prevents an undue amount of glucose from accumulating in this fluid. Hedon has shown, by passing the blood of normal animals through a depancreatized dog, that glycosuria may be prevented. This serves to show that the blood of normal animals contains some substance or substances which regulate carbohydrate metabolism.

The Relation of the Pancreas to Diabetes.

This evidence, when added to the facts about the islets to which we have already referred, is sufficiently convincing to warrant us in assuming that the pancreas possesses an internal secretion which, by its presence in the blood, regulates sugar storage, although its influence upon the glycogenetic properties of the liver has still to be determined. In this connection, Schäfer suggests that "the substance produced by the pancreas islets may be a chalonic autacoid which tends to inhibit the formation of glucose from glycogen, and incidently to promote the storage of glycogen, so that in its absence the glycogen which is present in the liver is rapidly converted into glucose, and the sugar absorbed from the alimentary canal formed in the body is not stored by the liver. The result again will be hyperglycæmia and glycosuria."[3] Schäfer proceeds to say that the "hypothesis that there exists a chalonic or inhibitory agent in the internal secretion of the pancreas which affects carbohydrate metabolism is probably the correct one."[4]

In any case, the evidence as to the part played by the islets of Langerhans in the production of diabetes is very complete; the discovery by Opie that a man who had died of diabetes possessed atrophy of these cells was a strong confirmation of the theory that these islets possessed some such function. This has been confirmed by numerous autopsies, so that one of the greatest authorities on this subject, Professor Van Noorden, now maintains that no diabetes can exist without disease of Langerhans' islands.[5] This author in the same place divides diseases of the islands into two groups: those which result from diseases of their environment, and those resulting from specific disease of the islands independent of their surrounding tissues. The first of these groups would include such affections as inflammatory conditions of metastatic origin, or inflammation proceeding up Wirsung's duct, and pancreatic arteritis; while the second group includes "congenital constitutional atony of the island system" and "acquired atony of the same system." In association with this classification—that is to say, in support of the idea that some cases of diabetes owe their origin to disturbances from without the pancreas—Morris believes that a bacterial infection from the duodenum may cause pressure upon the islets, and thus set up a pancreatitis. When the pancreatitis is relieved, the pressure disappears and likewise the glycosuria.[6]

The present writer has quoted these views for the reason that they offer a feasible theory as to the production of pancreatic diabetes in man, and give some idea as to the manner in which interference with Langerhans' islets may be brought about.

Apart from the interest of the recent discoveries which physiologists have made about the functions of the pancreas, these discoveries throw an added light upon the part which this gland plays in the general bodily metabolism, as well as its importance in supporting the hormonic balance. Again, our newly found knowledge explains many facts which were hitherto known as facts, but lacked an explanation. As an example of this assertion, we may mention one factor which characterizes glycosuria—namely, the increased liability to infection. It has been known for many years that the diabetic possesses little phagocytic power, and that he is not only a bad subject for operation, but also extremely prone to develope concurrent diseases, such as tubercle. Many observers have drawn attention to this fact, and have emphasized the lowered resistance to the tubercle bacillus which diabetics possess.

H. R. Harrower published an article in the *Practitioner*, in which he dealt very fully with the influence of the pancreas and its extracts upon infection; and he maintained that this gland is concerned with defending the body against bacterial infection. This is reprinted with additions in his recent book,[7] and the reader is referred to this chapter for an able and comprehensive account of this action of the pancreas.

In discussing the action of the pancreatic hormone, we must bear in mind that it, like all other internal secretions, has a relation to its fellow-hormones, and that some facts bearing upon this have been recently brought to light. Thus, it has been shown that the thyroid as well as the parathyroids influence pancreatic activity, but in opposite relations. The thyroid appears to be antagonistic to the pancreatic secretion, for its removal tends to prevent pancreatic diabetes;* while the removal of the parathyroids assists hyperglycæmia. We have already seen that there is an increased tendency to glycosuria in Graves' disease, while there is always an increased sugar tolerance in the opposite condition, submyxœdema.

Another factor which must be mentioned when discussing sugar metabolism is the permeability of the renal filter—that is to say, the amount which the kidney is capable of passing through its meshes. The normal sugar content of the blood is about 0·1 per cent., and to this amount the renal apparatus is impermeable. But if the amount exceeds this figure the kidney is unable to resist the hyperglycæmia, and sugar passes into the urine. A marked degree of hyperglycæmia is always present as the result of extirpation of the pancreas, and this is the immediate cause of the glycosuria. The immediate production of sugar in the blood in excessive quantities following upon removal of the pancreas is doubtless concerned with several facts which bear upon the hyperglycæmia. The glycogen in the liver is one of the first substances

* But see Chapter I., p. 29, for Gley's views on this subject.

to be altered by the operation, and this is very markedly reduced shortly after the removal of the gland. After generous feeding with carbohydrates, moreover, only traces of glycogen are able to be discovered. In contrast to this, the leucocytes exhibit a very high glycogen content. It is possible that this freeing of the glycogen reserves is one source of the increased amount of sugar in the blood, but it can hardly be the only one, for it would soon be exhausted. The additional sugar must come from albuminoids and fats, and this would in some measure account for the extreme wasting which these cases show.

So much for a few facts bearing upon the relation between the pancreas and the symptoms of diabetes. Now we will discuss a little more fully the internal secretion of this gland before turning to the therapeutic consideration of the pancreas.

Origin of the Pancreatic Internal Secretion.

It was at first supposed that, if an internal secretion existed at all in this gland, it was formed by the same cells which manufactured the ferments—in fact, that such cells performed a double action. In 1869 Langerhans first drew attention to those groups of cells which have since borne his name, and from their characteristics it is now assumed that they are responsible for the internal secretion. They are composed of badly defined polygonal cells, with large nuclei, and a very free blood-supply which comes from capillary bloodvessels in intimate relation to the cells. It is generally believed that these cells have no communication with the acini of the gland, but the question is not definitely settled. In some of the lower animals proof is forthcoming that there exists some connection between the excretory ducts and the cells of the islands.* Again, it is believed by some workers that the islets play a part in the production of the external pancreatic ferments, or, again, that the islets and the acini are not functionally differentiated.

The action of adrenalin upon pancreatic activity is of interest, for it is well known that adrenalin when injected into the blood-stream sets up a temporary glycosuria; but it is not equally well known that some observers have found that the administration of adrenalin to animals has been followed by the appearance of necrosed areas in the islets of Langerhans. Although the action of adrenalin in producing glycosuria is apparently mainly through the pancreas, that this is not solely so is evidenced by the fact that there is an increase of sugar even in depancreatized animals after the administration of adrenalin. Again, hyperglycæmia can be produced by means other than disorder of the pancreatic functions and the administration of adrenalin, such as puncture of the fourth ventricle and stimulation of the splanchnics.

A fact which is interesting from the promise of

* Some observers have been able to inject the islands through the ducts, while others have observed connections between lumina in the islands and the acini.

therapeutic possibilities in the future is that elicited by Zuelzer—namely, that adrenalin glycosuria can be overcome by the administration of pancreatic extracts and juices; for, whether due to an antagonistic action on the adrenal hormone or to its effects on the permeability of the kidney, it shows promise of further therapeutic developments.

It has been stated that adrenalin instilled into the eye of a depancreatized animal causes dilatation of the pupil, which does not occur in the normal animal, and this test has been made use of for the diagnosis of pancreatic diabetes, as it has been shown that it is likewise present in man in some cases of diabetes. In any case, it seems that it will not be long before further light will be thrown both upon the relation of the pancreas to the production of diabetes, and also upon the site of production and the more exact nature of the internal secretion.

Therapeutic Considerations.

We now come to a brief consideration of the therapeutic possibilities of extracts of pancreas. It has been necessary in this chapter to deal somewhat fully with diabetes, as the study of this condition is directly related to any consideration of the internal secretion of the pancreas; and our knowledge at the present time has been mainly gained by experiments in the production of hyperglycæmia and glycosuria and their relation to the pancreas.

In dealing with the therapeutic side of the pancreas, we must realize that a good deal of difference of opinion exists as to the efficacy or otherwise of this particular form of hormone-therapy. First, with regard to the administration of pancreatic extracts in cases of diabetes, Schäfer, writing doubtless from the experimental standpoint, says: "It is not found that pancreas extracts have the effect of antagonizing the results of pancreas extirpation; in this respect they offer a parallel to the negative results of suprarenal extracts in antagonizing the effects of adrenal deprivation."[8]

It must be remembered that it is not maintained that all cases of diabetes which are encountered clinically are of necessity due to pancreatic disorders, in spite of the opinion of Van Noorden, which we have already quoted. It is therefore only reasonable to assume that some cases of diabetes which we treat with pancreatic extracts may be due to causes other than pancreatic. If this is so, we must not expect to improve every patient suffering from glycosuria who comes under our care by the administration of pancreatic preparations.

The reasons why we may expect that this treatment will not be universally successful are summarized by Harrower as follows:

"First, not in every case of diabetes is the pancreatic factor present or prominent. Second, very few preparations of pancreas are made with the object of specifically supplying as much as possible of the islet substance. Third, it is no easy matter to supply the lacking hormone, for it is normally supplied continuously to the blood, and we have no means of knowing how much is elaborated, or, in disease, how much is lacking, in each case. Fourth, the antagonism of the chromaffin hormone must be considered; for the diabetes may be due not simply to a deficiency of the pancreatic internal secretion, but to an exaggeration of that of the adrenals or a combination of both. Fifth, evidently several other factors are concerned, and hence the hormone treatment of diabetes *alone* cannot be instituted with hopes of success."[9]

Having given the reasons why this method of treating diabetes is at present not entirely successful, we may perhaps be allowed to quote a few opinions which are favourable to pancreas-therapy. Thus, the same author a little farther on in the same chapter says: "It is evident that the pancreas ferment preparations may have an excellent influence upon glycosuria."[10] Harrower explains this thus: "This is probably due to the restorative action on the pancreas caused by the reinforcement of digestion, and the removal, in part or altogether, of the pancreatic disability, which is not alone reflected upon its external, but also on its internal secretion."

Again, Harrower refers to trypsogen (a combination of the ferments trypsin and amylopsin with the internal secretion) as having benefited several cases of undoubted diabetes mellitus; occasionally the sugar has quite disappeared, more often the symptoms characteristic of this complaint have been much benefited, weight has been increased, polyuria quite controlled, and sugar reduced."[11]

There are also on the market other preparations of pancreas, some of which are composed of one or more of the pancreatic ferments, while others are extracts of the whole gland. Before proceeding farther with the discussion of this form of therapy, we must emphasize that it is absolutely essential it should be regarded, in so far as diabetes is concerned, as an adjunct rather than as a sole form of treatment. For it is quite agreed that where there is excessive glycæmia there is every reason to relieve materially the strain upon the pancreas by limiting the ingestion of carbohydrates. Therefore, so far as this disease is concerned, diet should always be the primary consideration, and an endeavour to replace a lost or diminished internal secretion a justifiable secondary one.

Another preparation which contains the extracts of liver and pancreas is Kinazyme, and it is recommended by its manufacturers to increase weight; it is also said to be a valuable adjunct to the treatment of tuberculosis. It may be presumed that this not only is believed to encourage normal digestive processes, but also to raise the bodily resistance to infection.

It has also been stated that extracts of pancreas are useful in hypertension, presumably for their counteracting power on the chromaffin system. In cases where there is some evidence of hyperadrenia, such treatment should be given a trial.*

Finally, while insisting with as much stress as formerly upon dietetic and hygienic principles in the treatment of diabetic and kindred disorders, the practitioner should bear in mind preparations of this gland; for it is quite possible that such preparations will turn the scale in favour of the patient, while if left solely to the conservative method of withholding carbohydrate food it might turn in favour of the disease. Such therapy as is offered by extracts of the pancreas is rational and harmless, and it must be confessed that there is an opening for any form of treatment which will make the lot of the diabetic an easier one. For this reason alone, even if no other is forthcoming, it is advisable to try this form of opo-therapy in those diseases where it may be assumed that the pancreas is at fault; not only in definite diabetes, but in deficient digestion (the so-called carbohydrate dyspepsia), either alone or combined with preparations of the intestinal secretions, to which the pancreatic ferments have so close a relation.

* For further details of hyperadrenalism see Chapter XII., p. 244.

As opposed to this theory, some recent experiments on the relation between the pancreas and the adrenals state that the blood in the suprarenal veins contains less adrenalin after pancreatectomy than before, which may indicate that the functional loss of the secretion of the latter gland depresses the action of the former (*Endocrinology*, pp. 488-489).

These diseases, whose name is legion, offer a legitimate scope for the rational practice of organo-therapy, and so far as assimilation is concerned the pancreas may be regarded as the foundation, which, if upset, even by temporary or slight disturbances, is capable of upsetting the balance without which normal metabolism is impossible.

References.

[1] Halliburton, Handbook of Physiology, p. 491.
[2] Schäfer, The Endocrinic Glands, p. 125.
[3] *Ibid.*, p. 129.
[4] *Ibid.*, p. 130.
[5] Van Noorden, *Practitioner*, vol. xciv., No. 2, p. 237.
[6] Morris, *Jour. Am. Med. Assoc.*, lx., 1913.
[7] H. R. Harrower, Practical Hormone-Therapy, ch. viii.
[8] Schäfer, *loc. cit.*, p. 128.
[9] Harrower, *loc. cit.*, p. 104.
[10] Harrower, *loc. cit.*, p. 106.
[11] Harrower, *loc. cit.*, p. 107.

CHAPTER IX

THE SEXUAL ORGANS AND THEIR INTERNAL SECRETIONS

It will only be possible to review briefly the main features of the sexual organs and their hormones. For the subject is so vast, and the difference of opinion which exists about many of these organs and their secretions is so great, that it would necessitate a far too lengthy study here. We shall therefore enumerate the main facts with regard to the hormones elaborated by these glands, and deal briefly with the relations between these secretions and those of other of the endocrine glands.

For this reason, if some of the views may appear dogmatic, it must be remembered that we are unable, owing to limitation of space, to give the results obtained by different observers, but must content ourselves with an expression of the views which have obtained more or less general assent.

We have mentioned in previous chapters that an intimate relation exists between many of the sexual secretions and the hormones elaborated by some of the other ductless glands. As an example, the adrenals have an intimate relation with the ovaries and testes, and more than a few cases are recorded which bear this out.* Elliott mentions the case of a young woman, perfectly normal sexually, who at the age of twenty lost her menses; this was followed by the appearance of secondary sexual characteristics of the opposite sex, such as the growth of a beard and the development of a masculine type. Four years later she was operated upon and a tumour of the right adrenal gland removed.[1]

Again, a case described by Alberti shows a similar relationship, only the perversion is differently connected. The patient was a young girl who was perfectly normal sexually, but who gradually reverted to the masculine type. There was a loss of adipose tissue, the hair increased, more especially upon the body, the breasts became soft, and the voice deepened. A few years later she was operated upon for ovarian tumour, and eventually died of peritonitis. These two examples are selected, for they refer to relations between two different systems, and show that an intimate relationship does exist between the sexual glands and other of the internal secretory organs.

Internal Secretion of the Testis.

Recent experiments have shown that the internal secretion of the testis has a vast influence in animals belonging to the species which has a periodical rutting season, for changes in various parts of the body as well

* See Chapter I., p. 32.

as in the reproductive organs have been noticed at such times. If there is an internal secretion provided by the testis and the ovary, where is this formed? It is now believed that the "interstitial cells of Leydig" in the testicle, and the corresponding cells in the ovarian stroma, are the sites where this secretion is manufactured.

The interstitial cells are found between the seminiferous tubules, and vary in number. They are of mesodermal origin and appear at an early date of embryonic development, before the seminal cells have assumed their cytological character (Biedl). From the study of the development of sexual characteristics in cases of double cryptorchidism, from the effects of ligature of the vasa deferentia, and, from the study of tumours developing in the testis, it is believed that the interstitial gland, or organ of Leydig, is concerned in the production of the internal secretion of the testis and in the determination of the male sex characteristics. "It is evident, then, that the presence or absence of Sertoli's cells does not affect the secondary sex characters, and that the internal secretory function is the sole property of the interstitial gland. This gland not only exercises a protective influence, but it determines the appearance of the somatic male characteristics."*

The changes which appear at puberty owe their origin to an internal secretion which "sensitizes" the nervous reflexes concerned with the performance of

* Biedl, "The Internal Secretory Organs," pp. 394, 395.

the sexual act. That the various nervous reflexes are developed to a high degree of sensitiveness has been shown by experiments on frogs during the spawning season, which proved conclusively that these animals develope additional nervous mechanisms during the period of sexual activity.

Again, it has been abundantly established that a large number of internal secretions are concerned in the development of the sexual glands; for sexual precocity can be associated with tumours of the adrenals and with disturbances in the hormonic balance; while the influences upon sexual development which are exerted by the hypophysis have already been discussed in a previous chapter.[2*] It would seem, however, that the adrenal gland is especially concerned with the regulation of the sexual secretions, for, in some post-mortem examinations of cases of sexual precocity, out of seventeen such cases, and four surgical cases, suprarenal tumours were found in eleven, nine being girls and two boys.[3] There are many more such cases which have been published which certainly justify us in assuming that the relation between the genital glands and the chromaffin system is a close one, and morphologically this is to be expected.[4]

* "Souza and Castro offer an excellent study of the diseases produced by endocrine disfunctioning, in which the main symptoms are atrophy of the gonads and general trophic alterations. Their observations comprise twenty cases. The common link of them is atrophy of the sexual organs. Three of the cases had tumours of the pituitary body" (*Endocrinology*, p. 535).

The Uterus and Mammary Gland.

Now for a few words about the relation between the uterus and the mammary gland. There can be little doubt that the development of this latter organ depends upon a secretion from the genital apparatus. It was at one time thought that the connection between the uterus and the breast was a nervous one; but this has long since ceased to be believed, as experiments have shown that destruction of the nervous connection has no influence in inhibiting the flow of milk in a pregnant animal. The connection is therefore by means of a chemical messenger; and it is now believed that this messenger emanates from the ovaries, and not from the uterus, as was formerly supposed. Experiments have shown that the mammary gland does not develope after removal of the ovaries in young animals, but that transplantation of ovarian substance produces normal development.

Much work has been done recently upon the relation between the mammary gland and the pregnant uterus. The question to be solved is, From what source comes the hormone which activates lactation? Is it from the maternal or the fœtal organs? Does it come, as maintained by Halban, from the placenta, or does the fœtus provide it, or is it a product of the uterus or ovary? We have not space to enter into the details of the physiological work which has been done on this subject; we must therefore content ourselves with outlining the views of authorities.

Basch, from the results of experiments in which he injected placental extracts, came to the conclusion that mammary activity during pregnancy depended upon a substance found in the placenta. Starling and Lane-Claypon experimented with injections of fœtal extract, extract of uterine mucous membrane, and ovarian extract. They produced mammary hyperplasia by injecting fœtal extract, but the other extracts were inert in this respect. This has been confirmed by experiments carried out by Foa, and also by Biedl and Königstein.

Without entering into any further details of these experiments, we may quote in full the conclusion at which Biedl arrives on this subject, for it gives a good hypothesis upon which to base our views. "The secretion of the hyperplastic mammæ is not difficult of explanation. . . . The growth of the gland is the expression of an assimilatory increase of material with simultaneous inhibition of disassimilatory decomposition. The growing gland produces no secretion, or very little (colostrum). With the suppression of the assimilatory hormone supplied by the fœtus—that is to say, at birth or by termination of the pregnancy during the second half—disassimilatory decomposition, as expressed by the secretion, is enabled to proceed unchecked."[5]

We need not spend much time in studying the effects of castration upon development, for these are well known. There are, however, one or two facts which are important.

Effects of Castration.

The removal of the ovaries in young animals produces certain features of arrested development, among these being a rudimentary condition of the Fallopian tubes and uterus. It has been shown, however, that the transplantation of ovarian tissue under the skin remedies all these defects and the animal developes normally. This shows definitely that the controlling influence is chemical (hormonic), and not reflex. Again, the effects of castration upon young male animals, and upon youths, as is practised in the East, shows that there is a definite controlling agent in the secretion of the genital glands which, directly or indirectly, governs growth. Thus, changes take place in the bones, particularly in the skull and the pelvis, which produce an increase of growth, with retarded ossification of the epiphyses.

Pregnancy appears to be accompanied by reduced ovarian section, and it has been noted that young females grow during pregnancy, which, accompanied as it is by diminished ovarian secretion, would appear to show that the restraining influence of this secretion is temporarily removed. Or, to put it in another way, the sexual glands elaborate a hormone which is concerned in the ossification of epiphyses; if this be withdrawn before ossification is complete, increased skeletal growth ensues.

Again, castration affects the hormonic balance, as is shown in the changes which are produced in the thyroid, thymus, pituitary, etc., by removal of the testes: and Fichera showed, in 1906, that the enlargement of the pituitary which followed castration in animals could be reduced by the injection of extract of the testicle. Again, it has been shown that the thyroid under such conditions is atrophied, the thymus persistent, and the hypophysis enlarged. Only a few experiments have been performed on this aspect of the relationship of the genital glands with other of the organs of internal secretion; but in one instance of a eunuch dissected by Tandler and Gross these changes in the thyroid, thymus, and pituitary, were noted.

Again, the general metabolism is profoundly affected by changes in the reproductive organs; and the obesity, and in some cases mental sluggishness or other psychic changes which occur in senility, are too well known to require more than mention. Löwy and Richter investigated the metabolism in castrated animals, and showed that there was a reduction in proportion to body-weight, as well as a reduction in the total metabolism of the body.*

* Some experiments recorded by Wheelon and Shipley are instructive. The object in view was to demonstrate the relationship between the sympathetic nervous system and the internal secretion of the testis. These experiments showed that about six weeks after castration, pressure responses to nicotine averaged 50 per cent. lower than before removal of the testis. From two to three weeks after a testicular transplant there was a marked rise in the activity of the vasomotor mechanism. "The findings point to the conclusion that a direct relationship exists between the sympathetic nervous

The relation between ovarian secretion and osteomalacia has been the subject of much speculation. Biedl thinks that, while it cannot be maintained that we have definite proof of the causative rôle played by the ovarian secretion in the production of this disease the probability is that the ovary, rather than any of the other endocrine glands, such as the thyroid, thymus, etc., is the main gland concerned in the production of the disease; although there may be several glands concerned, the ovary is certainly the chief.

The pioneer work which Brown-Séquard undertook in administering to himself extracts of testicles, and the report which he made as to the results, may be said to have founded the theory and practice of organotherapy, however empirical this treatment was and, to a certain extent, still is. His results are very well known, and need not be stated here at any length; suffice it to say that he found his strength much increased by this administration, he was less liable to fatigue, his excretory apparatus was improved, and the effects were in general satisfactory. *Testicular* extract is said to contain nucleoprotein and toxic bases, and it has been stated by some observers that the results of administering such an extract to animals are widespread and important;* also it has recently

system and the primary reproductive organs. Castration results in a depression of the sympathetic mechanism, while the re-establishment of the lost parts partially reinstates normal activity" (Author's Abstract in *Endocrinology*, pp. 482, 483).

* I have recently received some reports of clinical experience with these extracts, which emphasize one aspect of their ad-

been said to play a part in the production of the genito-vesicular reflex (Serralach and Pares, quoted by Biedl). On the other hand, it has been stated that *ovarian* extract, when injected, lowers blood-pressure, causes in the thyroid gland a preliminary reduction followed by an enormous increase in volume, and reduces the volume of the kidney.

The Internal Secretions of the Sexual Organs.

As we have already said, the cells of Leydig are supposed to be the seat of formation of the internal secretion of the testis; and an interesting fact in connection with this is that puberty produces an enormous development of these cells, while old age sees a marked degree of atrophy of the same cells. It is stated that, in those cases where cryptorchidism in man is associated with the development of secondary feminine characteristics, there is complete sclerosis of the testicle, and that the cells of Leydig are reduced to a few scanty groups (Biedl).

The influence which the ovarian internal secretion exerts may be studied from two standpoints: first, its place in determining the sex characteristics, and second, its relation to other bodily hormones.

It has usually been acknowledged that the secretions

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ministration—namely, that they are liable to increase the blood-pressure. If this experience is confirmed, their utilization should be accompanied by a careful scrutiny of the vascular system.

of the gonads determine the sex characteristics, and that the menstrual cycle is regulated by hormones which are secreted by the ovaries. In animals it has been shown that the catamenia occurs when the ovaries are transplanted (Marshall and Jolly), which indicates that this function is not regulated by nervous controls. Again, experiments have proved that œstrus occurs in animals in whom the spinal cord has been divided, and a case is on record in which a woman became pregnant with complete transverse lesion of the spinal cord.

In speaking of the influence of the ovary on the sex characteristics, Blair Bell says: " . . . It is commonly held that the genital organs, and more particularly the gonads, contribute the primary sex characteristics, and that the secondary sex characteristics are dependent on internal secretions arising from the gonads in question—male or female as the case may be. . . . It is well known that every person is partly masculine and partly feminine, that in each case are to be found, especially in connection with the genital ducts, relics of the opposite sex, and that during the first few weeks of fœtal life it is not possible to identify the trend of sex development. . . . About the end of the fifth week of fœtal life it may be possible to decide whether the gonad is to be an ovary or a testis; hitherto it has been an indifferent organ, so much so that the cause of development in the Gartnerian (primary excretory) and Müllerian ducts, especially in the latter, may give the first indication of sex determination. . . . It appears probable, therefore, that normally the sex development of the ducts is not primarily dependent on the nature of the gonad. In other words, the character of the sex pervades all the tissues of the fœtus, including the sex gland itself."*

The relation of the ovarian secretion to other internal secretions is intimately mixed up with the influence of the gonads in general upon metabolism, and this we have already discussed.† It is not too much to say that the ovarian secretion is of vital importance to the individual, both from the mental and physical standpoint; and in this relation the ovary is analogous to the testis. We have already seen that changes are produced in such distant organs as the thyroid, thymus, and pituitary, by removal of the testes, and similar results are noted after removal of the ovaries. After the normal menopause, which is usually gradual, changes similar in character take place, and Blair Bell is of the opinion that "the more sudden the climacteric the worse the effect."‡

The influence of the ovarian secretion upon the mammary development is more marked before puberty than after, castration before puberty preventing glandular development. The inter-relationship of the gonads with the other internal secretions forms one of the most interesting albeit intricate problems of endocrinology. We have already glanced at these rela-

* "An Address on the Nature of the Ovarian Function," by W. Blair Bell. *Lancet,* October 30, 1920, pp. 879, 880.

† Chapter I.; see also preceding pages.

‡ *Loc. cit.,* p. 881.

tionships, but perhaps we may enlarge somewhat in this chapter upon the action and interaction of the gonads and the other hormones.

Oöphorectomy produces changes in almost all the ductless glands. In animals, before puberty, it results in mal-development of the uterus, and disease or removal of the ovaries is usually accompanied by loss of the feminine characteristics, and, in some cases, the development of male features. It would seem, therefore, that there are potentially male characteristics which remain latent so long as the ovarian secretion is active. The experiments of Marshall and Jolly throw further light upon the importance of this secretion to the normal menstruation. These observers showed that if, after oöphorectomy, part of the ovarian substance is transplanted, the tissues may survive and atrophy of the uterus does not occur. Ova may be formed and menstruation continue. The grafts are more successful if the tissue comes from the animal itself, rather than from another animal.

Steinach's observations on rats show that the ovarian tissue plays an important part in the formation of the femininity of the body. He transplanted ovarian tissue into young castrated male rats, producing the "characteristic slight bony development, the growth of the finer hair of the female, the development of mammæ and nipples, and the appearance of two peculiar female reflexes: (1) 'The tail erect reflex'; and (2) the peculiar kicking, guarding reflex to keep the male off before the full development of œstrus.

These feminized rats were followed by males as if they were female."*

The effects of removal of the ovaries upon metabolism in general are widespread. There is a decrease in the respiratory exchanges of 14 to 20 per cent.;† the normal is, however, restored by the administration of ovarian extracts. Adiposity develops, the thyroid undergoes change, "the sympathetic control, too, always somewhat unstable in women, becomes more variable owing to the changes that take place in the calcium metabolism, which is so largely concerned in the reproductive processes."‡

The thyroid appears to assist the gonads, for thyroidectomy arrests their growth. The pituitary has a similar relation, for its destruction produces atrophy of the sex glands; inversely castration, it should be noted, causes pituitary hypertrophy. Reference has already been made to the close relationship existing between the adrenal bodies and the gonads, and we have quoted the views of Sajous on the part played by adrenal tissue in regulating the sexual functions. We have also indicated the metabolic disturbances which follow castration, and drawn attention to the resemblance between these and the general features of hypothyroidism and hypopituitarism. The relation between the thymus and the ovary is less clear than that existing between the former gland and the testis—namely, a supplementary action. The thymus exercises

* Noel Paton, "Regulators of Metabolism," p. 153.
† *Ibid.*, p. 161. ‡ Blair Bell, *loc. cit.*, p. 882.

a controlling action on the gonads, but it co-operates with the latter in stimulating growth and development.

There is a suggested relationship between the parathyroids and the gonads, as the symptoms of hypoparathyroidism are increased by pregnancy (Paton).

Without going farther into the physiology of the gonads, it is sufficient to say that there can be very little doubt that these organs play a vital part in the production of secretions which, although we are ignorant of their full importance, are necessary for the development of a normal individual: not only in so far as sexual characteristics are concerned, but even with regard to the adequate working of metabolism.

The secretions of the prostate are likewise not fully understood, certainly so far as its internal secretion is concerned. Its external secretion exerts an influence upon the spermatozoa, and dilutes the testicular fluid; but little is known of the properties of its hormone, except that injections of prostatic extract made from animals are extremely toxic. Therapeutically, extracts of prostate gland are not prescribed much in this country, although they are supposed to be beneficial in post-operative melancholic conditions following removal of this gland.

Therapeutics of the Sexual Glands.

We must now turn our attention to the therapeutic possibilities of extracts of the genital glands, and we shall endeavour to give a résumé of the possibilities of such therapy.

A very wide range of treatment is open for the administration of preparations made from the gonads, and it is now established that, in conjunction with other organo-therapeutic preparations, should these be indicated, a great deal of benefit may accrue to patients suffering from a variety of diseases which it would be difficult to ameliorate by other means.

Let us commence our study by considering the help which may be given to that very widely encountered disease, neurasthenia. It has been conclusively proved that the exhibition of some preparation of the testes (such as Spermin) has the power of raising the amount of muscular work available, of increasing the strength of the individual, and of banishing ready fatigue. In other words, the conclusions arrived at by Brown-Séquard have been substantiated, and it is now believed that the administration of testicular preparations is followed by improvement in these cases. Some manufacturers combine this substance with other secretions in the form which Leonard Williams aptly calls a "mitrailleuse."

Unfortunately, there appears to exist some degree of opposition to this remedy, and in consequence it has never been widely used. There is, however, a good deal to be said for its powers, and Harrower summarizes its utility in the following words:

"A course of treatment with testicular extract frequently accomplishes such a number of changes of such remote organs, and influences such widely disconnected ones, that to report actual results might even be sufficient to discount the position of this method. The extent of these results is undoubtedly due to the stimulating action of the testicular hormone upon the endocrinous system as a whole, and as a means of revitalizing an individual with deficient oxidation, poor nutrition, nervous inactivity, and general weakness, the system is of undoubted value. There are few single remedies which can compare with active and properly prepared testicular extracts."[6]

The therapeutic possibilities of the ovaries are numerous. Thus, it is well known that an intimate relation exists between the pituitary gland and the ovaries, and consequently, in undertaking the treatment of disorders of the pituitary, this fact should be remembered. The administration of ovarian extract is worthy of trial in such cases, more specially where the symptoms point to excessive bony growth (it has already been said that the ovary is presumed to exert an influence on the ossification of the epiphyses). In this connection Blair Bell, speaking of imperfect development, says:

"Nearly all the patients are adipose, whether the deficiency arise in the thyroid, pituitary, or ovaries. If there be pituitary insufficiency, the skin will be found to be soft and smooth; if there be thyroid insufficiency, it is harsh and rough. With pituitary insufficiency the blood-pressure tends to be below 110 mm. Hg; but with thyroid insufficiency it is usually normal (125 mm. Hg), or slightly above normal."[7]

Further, if it be true that both thyroid and pituitary insufficiency induce ovarian insufficiency, then we can, as Blair Bell points out, treat the ovarian deficiency by means of either thyroid or pituitary extract. This simplifies treatment in so far as this class of disorder is concerned; but, nevertheless, for other instances of ovarian deficiency, such as are exemplified in derangements of the catamenia, ovarian extract will be found to be very useful. Blair Bell also drew attention to the influence of the ovaries upon calcium metabolism, and showed that the calcium in the urine was diminished after oöphorectomy by one-half;[8] which again bears out what we know with reference to the beneficial effects which sometimes follow in cases of osteomalacia when double oöphorectomy is performed.

Ovarian extract has been utilized in the treatment of such disorders as chronic rheumatism, gout, and fibrositis. Psoriasis, often associated with such diseases as these, has been treated with this extract, and some authorities have claimed good results. Some degree of correlation has been noted between the appearance of psoriasis and the alteration in the regularity of the menstrual flow.

Harrower says that better results are obtained by the exhibition of extracts of the corpus luteum than are recorded by the ingestion of extracts of the whole gland; and other observers are of the opinion that the superiority of this extract over the total extract of the gland is incontrovertible. Extract of corpus luteum will be found useful in neurasthenia in women, in difficulties arising at the menopause, after removal of the ovaries for cystic or other disease, and in conjunction with thyroid or pituitary for incomplete development, etc.

Several writers, notably Leduc and Blair Bell, lay great stress upon the calcium metabolism of the body, and its relation to disorders of the nervous system (neurasthenia, hystero-epilepsy). Thus, we know that there is a storage of calcium salts in hypothyroidism, and an increase in the calcium metabolism in Graves' disease; also that at times like the menopause a disturbance of more than one gland may take place. The signs in any individual case may point to which of the endocrinous glands is chiefly at fault; but the best results are probably obtained, as Blair Bell points out, by the administration of ovarian extracts, in company with whichever of the other glands appears to be at fault. Again, this writer suggests that the mental depression from which some women suffer at the climacteric can be much relieved by the administration of thyroid extract. This in itself would point to the thyroid as being one of the glands deficient in secretion at the menopause.

One more fact in connection with the ovaries, and we can pass on to the consideration of other secretions. It is assumed that menorrhagia may be due to excessive action of the ovaries—*i.e.*, hyper-oöphorism, with which may be associated hyperthyroidism. If this may be presumed to be so in any given case, it is obviously wrong treatment, and may even do harm, to administer ovarian extracts; for the same reason extract of thyroid gland must be avoided. On the other hand, where amenorrhœa is present, especially where the appearance of the menses at puberty is delayed, we may with advantage prescribe thyroid extract with or without ovarian extract, remembering the stimulating effect which this extract exerts upon this function. Therefore, where obesity is associated with amenorrhœa the possibility of hypo-oöphorism should be borne in mind.

We must refer in passing to the mammary gland, and state briefly the modern conception as to its utility as a therapeutic agent. We have already pointed out that Starling and Lane-Claypon experimented with fœtal extracts, and came to the conclusion that such extracts were capable of producing hyperplasia of the mammæ. Therefore it would seem from this that the fœtus is the seat of formation of a hormone which stimulates the secretion of the breasts. That there is a close relation between the uterus and the mammary gland has been known for a long time; what that relation is we are better able to say now than formerly. The obvious connection between the functioning of the breast and the uterus is exemplified by such occurrences as the enlargement of the mammæ at puberty and pregnancy, the intimacy of its nerve connections, and the pain in the breasts during menstruation. The following facts also bear upon this study: the placental hormone, to which we have already referred, when injected into another animal, produces a flow of milk; and this will likewise take place in transplanted portions of the gland.

The relation of the ovary to the mammary gland has something in its bearing of an antagonistic nature. Thus, although complete ovariotomy may result in disappearance of the breasts, which latter glands will reappear upon grafting ovarian tissue, some observers believe that ovarian secretion is antagonistic to mammary. In this connection it is interesting to note that some investigators have found that the rupture of the ripe follicle of the ovary results in the growth of the mammary glands.

From the therapeutic standpoint, moreover, the balance of evidence is in favour of administering mammary extract to promote lactation. It is also stated to be useful in combating dysmenorrhœa and menorrhagia; it is not improbable that it is able to render aid to the uterine functions, either on account of its supposed correlation with the thyroid gland, or on account of the known sympathy which exists between the mammæ and the uterus.

We have now outlined the facts with reference to the reproductive glands and their internal secretions, and we have indicated the lines along which treatment of these disorders may be conducted.

References.

[1] Elliott, *Practitioner*, vol. xciv., No. 1, p. 132.
[2] Chapter I., pp. 31, 32.
[3] Biedl, The Internal Secretory Organs, p. 371.
[4] Chapter I., p. 32.
[5] Biedl, *loc. cit.*, p. 376.
[6] Harrower, Practical Hormone-Therapy, p. 341.
[7] Blair Bell, *Practitioner*, vol. xciv., No. 2, p. 270.
[8] Blair Bell, The Genital Functions of the Ductless Glands in the Female, *Lancet*, 1913, i. 809.

CHAPTER X

THE INTERNAL SECRETIONS OF DIGESTION

No book dealing with the ductless glands and their internal secretions would be complete without due reference to the part played by chemical messengers in the processes of digestion. For while our knowledge in this field is very incomplete, we know now that many of the factors which contribute to normal digestion are chemical, and not, as was thought, nervous in origin. It was previously assumed that the functions of digestion were regulated by either the sympathetic or central nervous system, and the influence of hormones was unrecognized. But recent work on digestion has shown that even in this field the work performed by autacoids is by no means unimportant.

For this reason, therefore, we propose to discuss briefly the internal secretions concerned in digestion, and to outline the main features of their work. We shall also, wherever possible, draw attention to any relationships which may be presumed to exist between the organs of digestion and other glandular structures of the body.

The salivary glands have been supposed to secrete a hormone which plays a part in digestion, either by stimulating the later stages of digestion or by carrying on salivary digestion in the stomach. There is now no doubt that this stage of digestion continues in the stomach, certainly in that part of the bolus which remains alkaline—that is to say, until it is soaked through with the gastric juices; and therefore the main work performed by the ferment may be said to be carried on in the stomach.

Again, certain authorities lay stress upon the parotid juice, and the possibility that it may be influenced by chemical messengers; while some clinicians have worked with preparations of the salivary glands, and have reported that they have influenced some of the abnormal conditions arising in other and remote organs. Thus, they have been used for ovarian disorders (the close connection existing between the parotid gland and the gonads is shown by the metastatic inflammations arising in the course of parotitis in the testicles and ovaries), and have been said to do good. Apart from this, which we have mentioned in passing, there is no evidence, not even presumptive, that the salivary glands are useful from the therapeutic standpoint.

The Gastric and Intestinal Secretions.

When we turn to the question of gastric and duodenal digestion, we find that we are at once in quite a different position. At the risk of wearying our readers, we will briefly recapitulate the work which led to the important discovery that pancreatic digestion is dependent upon chemical stimulation.

Following upon the researches of certain observers, it was discovered that the introduction of dilute hydrochloric acid into the alimentary canal was followed by a marked increase in pancreatic secretion; that this was due to the acid coming into contact with the walls of the duodenum; and that this produced a hormone which possessed the property of stimulating pancreatic secretion. It was the discovery of this last factor, a discovery made by Bayliss and Starling in 1902, which may be said to have laid the foundation of our present knowledge of the importance of the chemical messenger in keeping that balance in organic metabolism which alone can produce perfect health.

This substance has been named "*secretin*," and is released from its precursor *pro-secretin* by the entrance into the alkaline duodenum of the acid chyme. This substance, which has been called the principal alimentary hormone, is present in all animals, and is not only a human property; in fact, it has been stated that the human intestine is relatively and actually lower in its secretin-content than is that of the sheep.[1] An analogous secretion is furnished by the pyloric walls, and has been called gastric secretin or *gastrin;* and it acts upon the oxyntic and peptic glands of the stomach. Edkins was the first to demonstrate the presence of this substance in the stomach, and to show that its object is to stimulate into activity the secreting cells of the stomach. This hormone has a precursor, known as *pro-gastrin,* from which the hormone is formed, either by the products of digestion or by other stimulus.

In this way, then, do we find that a chemical messenger exists to activate from latent chemicals an active substance; and that in both cases—the gastric and the duodenal—the key which unlocks this chemical is a normal and usual concomitant of digestion. In the case of the duodenal "secretin," the acid unlocks the secretion either by neutralizing a substance which inhibits the flow of secretin, or else by directly producing the substance "secretin" from its precursor "pro-secretin." Whichever is the case is not a matter which need detain us here, and we will pass on to discuss other properties of this important hormone.

It appears that secretin acts not only on the upper intestinal tract in producing pancreatic secretion, but also on the lower intestinal walls—*i.e.*, the ileum—and assists in the production of *succus entericus.* It likewise stimulates bile production, and it is said that the typical stools of jaundice have been rendered normal in colour by a few doses of secretin. In this way, therefore, this substance may be regarded as an excitant of the motor functions of the bowel; for it has a laxative power partly dependent upon its action upon the intestinal juices and partly owing to its action in increasing the normal laxative, the bile. But it is necessary that a certain element should be present in the blood, for Hustin has shown that secretin alone is incapable of stimulating the pancreatic juice in the absence of blood. "The pro-secretin of the duodenal wall is first changed into secretin by contact with hydrochloric acid; it is then carried in the blood-stream to the pancreas, where, as a result of chemical change, its characteristic features are lost, secretin combining with amylopsinogen and steapsinogen, to form the ferments amylopsin and steapsin, and with the precursor protrypsinogen, to form trypsinogen. This last becomes the ferment trypsin only after it has come into contact with the entero-kinaise in the intestinal canal."* [2]

It will be seen from what we have already said that the acid content of the stomach is of great importance in the production of the secretion of the pancreas, and to a lesser degree of the other intestinal and hepatic secretions. It will also be seen that it is not unlikely that much of the good which has long been recognized to accrue from the prescription of acid mixtures in dyspeptic and constipated subjects may in reality, as pointed out by Harrower, be due to the release by such acids of the internal secretions of the bowel and stomach. The hydrochloric acid of the gastric mucosa has several important functions to perform, among these being its work as an antiseptic, its work in opening the pyloric sphincter, its power to activate pepsin, and lastly its action as a stimulant to the

* Although this is believed to be the sequence of events, there is still some divergence of opinion on the subject.

pancreatic secretion. In its absence pancreatic digestion cannot be carried on, for secretin cannot be formed from pro-secretin.

Although the facts which we have related with regard to secretin are well known and generally admitted as proven, little is known as to the actual constitution of this substance. It is not a ferment, but exactly what it is we do not know. It is, like the other hormones, a substance of low molecular weight, and, as we have already seen, it stimulates the formation of all the ferments of the pancreas. Its work in the complex scheme of digestion is balanced to a nicety. Thus, it is not secreted until there is work for it to do—in other words, until the food has entered the duodenum in its acid state; thus, there is no chance that it will irritate the walls of the intestine by producing pancreatic ferment-action in the absence of food. Even so, trypsin is not formed until it meets entero-kinaise, which again is not formed until food is present.

There is no positive evidence that secretin stimulates the internal as well as the external secretion of the pancreas, for it has yet to be proved that there is an absence or diminution of secretin in diabetes. In fact, it has been shown in one case of diabetic coma that there was abundant pro-secretin in the body.[3]

Turning now to another intestinal secretion, the succus entericus, there is still some question as to its formation. Pawlow thinks that its formation depends upon two factors, the distension of the bowel and the presence of pancreatic juice. Succus entericus contains several ferments: *entero-kinaise*, which acts upon the trypsinogen of the pancreatic juice; *erepsin*, which completes the digestion of proteids; and several sugar-splitting ferments. There is a good deal of dissension as to the exact nature of its formation, some observers believing that it acts as its own hormone, others that it is stimulated by the pancreatic juice, while others believe that additional factors other than those mentioned are required to bring about the secretion of this juice. As regards the proteolytic action of the intestinal juices, these latter require the presence of pancreatic juice to exert this action.

Turning now to other secretions of the alimentary canal, we must refer in passing to the supposed secretion of the appendix, also to that which it has been suggested emanates from the lymphoid tissue of the intestine, such as Peyer's patches. Some observers believe that the appendix secretes a hormone which stimulates peristalsis, and in support of this they quote the constipation which in some cases follows the removal of the appendix as proof that a normal intestinal excitant has been removed or inhibited. There is no definite proof of this, although the future may show that in ruthless appendicectomies we are removing a necessary stimulant, in spite of the fact that so many regard this organ as a useless relic.

The Liver.

The liver, whose chief function is the production of bile, nevertheless performs many other and important functions which contribute to the normal working of the body. For many years observers have been struck by the enormous size of this gland, which, they argued, could hardly be justified by its bile-producing properties alone. This was before its storage and filtering functions were realized; and, even after the facts collected by the experiments in which Eck's fistula was utilized, much remained to be explained as to the rôle which the liver played in bodily metabolism. We have now reached the stage where we have to consider whether the liver possesses an internal secretion, and whether extracts of this organ can be utilized therapeutically.

Let us first summarize the functions of the liver, and with the facts thus gleaned at our disposal we shall be better able to form an opinion as to the secretions produced by this organ. The hepatic cells are responsible for the production of the bile, with the bile-salts, pigments, and ferments; they are also concerned in the regulation of the sugar content of the blood, and in the regulation of nitrogenous metabolism; they are concerned, however, in regulating the power of coagulation of the blood, and they appear to have a definite rôle in the destruction of toxins, and in the prevention of such material from reaching the cells of the body. In this latter relation they act as filters between the gastro-intestinal tract and the general blood-stream.

We see, therefore, that modern physiology teaches us that the liver has other functions to explain its vast size beyond the mere production of bile. What evidence, then, have we that it possesses an internal secretion? It would seem that the secreting powers of the liver are analogous to those of the pancreas, inasmuch as they depend upon stimulation by chemical means for the adequate working of their secretions. This has been shown by experiments which have proved that all the nerves to the liver can be cut without interfering with the biliary secretions, and that excitation of the cut nerves does not influence the secretions either by accelerating or retarding such secretions. We saw when discussing the pancreatic secretion that it was stimulated by the production of secretin from pro-secretin in the presence of the acid chyme—*i.e.*, that it was dependent upon a humoral messenger—and in like manner may we assume that the secretion of the liver is affected. Indeed, we know that the production of bile is increased by secretin, and that other of the digestive juices are stimulated by this same hormone. If this secretion of the liver is stimulated by a hormone, it is more than probable that others emanating from the same gland are also so activated.

Therapeutics of the Digestive Secretions.

The extreme value of cod-liver oil has been known for many years, but only recently has it been recognized that it must owe its power to something more than its fat-content. In fact, recent work has shown that some of its value can be removed by processes of refining. Leonard Williams, speaking of the properties of cod-liver oil, lays stress upon this aspect of its value, and says: ". . . it is very probable that this biliary secretion of the cod, when introduced into the human economy, acts as a stimulant to one of the normal internal secretory glands, and that the secretion of the one so stimulated is inimical to the development of the tubercle bacillus. . . ."[4] This shows us another reason for its great value in tuberculosis, and explains its power of building up the body, while preventing toxins from reaching remote organs.

Other observers have experimented with cod-liver oil, and have sought to show that it is not the animal fat which it contains, so much as other less recognizable constituents, to which it owes its value. The internal secretory theory of the liver extracts certainly opens the way to many new applications of hormone-therapy and also explains many hitherto unexplained facts about the value of such substances as cod-liver oil.

Here we must leave this subject and pass on to a brief study of the value of extracts of liver. For some years such extracts have been used on the Continent, and many observers speak highly of their beneficial influence in countless morbid conditions. Thus, Gilbert and Carnot, of Paris, have studied this subject intimately, and have arrived at certain conclusions about this organ and its secretions. Others, following on these lines, have arrived at similar conclusions, and we will here refer briefly to one of the theories about the liver which has been recently expressed. Some of the workers in this subject believe that the liver possesses an internal secretion which filters the blood coming from the digestive tract, and neutralizes, or renders harmless, toxins emanating therefrom. This is supposed to be due to some chemical present in the liver cells itself, and not only in the bloodstream. In this way the liver may be regarded as a vast filter standing between the chemical exchanges occurring in the gastro-intestinal tract—which may possibly be harmful if admitted into the systemic circulation without due filtering—and the body. It is only to be expected that the organ which has such important work to perform should be large, and these and other recent views (even if not at present established beyond criticism) nevertheless help to explain the work which this gland is called upon to perform.

Before discussing the value of liver extracts, let us consider for a moment the therapeutic properties of secretin. It will at once be obvious that, provided this chemical can be prescribed for oral administration, and that when taken in this way it still exerts its characteristic influence, we have to hand a remedy of the very greatest possibilities.

Now, it appears that secretin-containing preparations can be so prescribed, and that they are active when taken by the mouth. As we have already seen, secretin requires an acid medium for its production and that in the absence of an adequate degree of gastric acidity the normal secretion of this substance cannot take place. It would seem, therefore, that in cases where hypochlorhydria is suspected, especially where secondary digestive disturbances are present, the administration of an acid mixture with meals might be sufficient to insure the production of an adequate amount of secretin.

This is one aspect of the subject, and, there can be little doubt, an important one; for the benefit which so often accrues from an acid mixture taken about meal-times is frequently out of all proportion to what might be expected, if we only regard it as an adjuvant to gastric acidity.

Another question which arises is, Can we give secretin by the mouth? Undoubtedly the preparations which are on the market achieve excellent results in many cases, and the dry secretin-containing tablets and powders appear to exert a beneficial action in a wide variety of cases, which range from intestinal meteorism to glycosuria. But the dose of the substances requires regulating, as many observers emphasize the fact that small doses often succeed where large doses fail.

Secretogen, which the makers describe as "the master-key which unlocks the alimentary glands," is such a preparation, and many excellent results have been reported after its use. Again, secretin is sometimes combined with extracts of other alimentary glands, such as the liver, pancreas, spleen, etc.

It seems to the present writer that these preparations find a particular field of usefulness in those cases where intestinal symptoms are combined with signs indicative of pancreatic or hepatic insufficiency. Thus, intestinal stasis in combination with glycosuria would be a condition where a secretin-containing preparation might improve the symptoms in a quite remarkable manner, for it might in very truth "unlock" the duodenal hormone (or replace it so far as its pancreatic stimulus is concerned), and thus start the alimentary secretions, stimulating in its turn the bile, succus entericus, etc., and supplying the missing hormone, the absence of which may have produced the entire syndrome.

From this, let us turn to the consideration of the value of prescribing liver extracts, and here we have to accept the testimony of those who have worked on these lines, and they are not numerous, as certainly in this country such administration has not been widely supported.

First of all we must enumerate the actions which liver extracts are supposed to possess, and the disorders in which they have been employed. Hepatic extract has been employed in functional disturbances of the liver, in those cases not always recognized in textbooks of medicine, but which are very well known in practice, and to which we may refer as "congestion of the liver," "hepatic inactivity," or "hepatic insufficiency." We may assume that in such cases, and it must be emphasized that we are referring only to functional disturbances of this organ, for some reason the secretion of the hepatic cells (not only the bile) is deficient, and that possibly not only is the conversion of the products of digestion incomplete, but that the filter-function of this organ is deficient. It used to be supposed that the symptoms of a "congested liver" owed their presence to bile in the blood-stream; but in the light of recent work it is much more probable that other and more complicated processes are responsible.

Extracts of liver have been prescribed in such cases, much along the lines that other glandular extracts have been prescribed in diseases which we have already discussed—that is to say, with a view to stimulating the production of the necessary secretions, and to prevent the appearance of the symptoms which we know must appear if the absence of the secretion concerned is allowed to persist. But this is only one example of the uses to which these extracts have been put. Hepatic cirrhosis has been treated by the administration of liver extract, and, more especially in the atrophic variety, has met with some degree of success.

It has been stated that such administration has a marked action upon nutrition, and assists the urinary excretion, and that favourable results have followed its use in cirrhosis of the liver, as well as in functional congestion, and even in cancer. It is only rational to assume that, provided it can reach its goal without being destroyed on the journey, it will have the power either to replace normal secretion, or to stimulate that part of the secreting mechanism of the organ which has not been destroyed. That it must have some action in replacing the deficiency has been shown by those observers who have demonstrated that the changes in excretion alone have been marked after the use of these extracts. Thus, they have shown that the urea index is markedly increased, as well as the total quantity of urine; that anasarca has diminished, and that the tendency to hæmorrhages, which is common in cirrhosis, has been lessened.

Again, its use has been recommended in cases of hepatic diabetes, and where the diagnosis has been accurately made its employment should do good. Harrower suggests that a good plan to adopt when in doubt as to the nature of glycosuria is to commence treatment with pancreatic preparations, and to administer these for one month, and then if no favourable result be obtained to try liver preparations. He goes on to emphasize that the form of diabetes associated with liver disturbances has peculiar characteristics, notably that the glycosuria occurs at definite times, as after a meal or in the evenings; that the major symptoms of the complaint, such as thirst and polyuria, are not so marked, but that the tendency to infection and gangrene is well seen. From this he infers that the liver is failing in its antibacterial powers. It is in these cases, according to this author, that hepatic extracts are useful.

It will be quite obvious that in so far as the treatment of diabetes by liver extracts is concerned, diagnosis is the essential point; and that whatever reliance be placed upon opo-therapy, general medicinal treatment should be insisted upon. For, as we have said elsewhere, the more we learn about this important subject, the more are we impressed with the fact that a regulated diet (in order to spare, so far as is possible, strain upon those organs concerned with sugar metabolism) is the first and most important point.

The dose of liver extracts is variable, but most authorities are agreed that it should be administered in generous and regular doses. It is said that extract of this organ, administered orally or per rectum, is practically non-toxic, and that it may be given in doses ranging from 15 or 20 grains of the dried extract every hour, and increased to as much as 60 grains three or four times daily.

A few words about bile may not be out of place here. Bile has been administered to patients suffering from "sluggish liver," and with excellent results. It has been shown that the administration of even small doses of bile is followed by a marked increase in the amount of bile secreted; and it is along these lines that treatment by biliary extracts has been followed. It certainly seems more rational to administer the normal stimulus than to irritate the papilla of Vater with calomel. For relatively small doses of bile extract are cathartic—*i.e.*, a dose of 10 grains—while 5 grains in repeated doses has a laxative effect. The administration of the biliary extracts is followed in many cases by the disappearance of the signs of intestinal putrefaction, such as meteorism and the passage of offensive flatus, and by the re-establishment of regular and formed motions. Bile, although not in itself an antiseptic, acts in the intestine as such, for it prevents stagnation by its power of stimulating the secretions of the bowel.

In conclusion we must refer to the hormone elaborated by Zuelzer, and placed upon the market under the name of "Hormonal." This observer examined gastric mucous membrane, and after many experiments succeeded in discovering a substance which proved to possess the power of increasing peristalsis. Further, he found that this substance was elaborated in the stomach and small bowel during digestion, carried in the blood, and for the most part stored in the spleen. As a result of experiments it was found that this substance, when injected into the blood, produced a marked increase in peristalsis. In another chapter we deal more fully with this hormone, so that at this place we will content ourselves with saying that the administration of this substance was followed by certain symptoms of an undesirable character, and that its use was discontinued in favour of "*neo-hormonal,*" which is stated to be free from the objectionable features. *Neo-hormonal* is usually given by intramuscular injection, but it has recently been given by the mouth, and the results have been promising.

It is probable that the stomach and duodenum produce a substance which has the power of stimulating intestinal movements, and that this hormone is largely responsible for the regular and daily evacuations which are characteristic of health. If further experience shows that *neo-hormonal* can rectify an intestinal musculature which has become sluggish, it will prove of the greatest value to therapeutics.

Among the abdominal organs which have been said to influence digestion is the spleen. The exact function of this organ is still shrouded in mystery, although certain attributes are now recognized. That it is concerned in the formation of certain of the white corpuscles, notably the lymphocytes, is now admitted, while it is believed that it also manufactures large mononuclear leucocytes. It is said to be the filter which removes broken-down corpuscles, both red and white, and it also drains the blood-stream, but its hæmopoietic function has long been established.

The question which concerns us here is, How is the spleen related to digestion? It would appear that it exerts a definite if somewhat remote effect upon digestion, for experiments upon animals have shown that splenectomized animals do not obtain nourishment from their food in the same way that normal animals do. In other words, this organ enables the main digestive glands to perform their work more adequately than is possible in the absence of the spleen.

It has been assumed from the results of these and other experiments that, while the spleen is not an organ that is essential to life, its purpose is partly to regulate the blood-stream and its contents, and partly to influence digestion, although our knowledge of its exact action in this latter respect is nil.

An inter-relation is suggested by the fact that the spleen has been found to be enlarged after removal of the thyroid; but Biedl says that this cannot be regarded as typical.

Its function as a filter is clearer, for does not the spleen enlarge in many acute infections, notably enteric ? It is possible that it is concerned in preventing the products of intestinal fermentation from remaining in the blood-stream, and that it secretes a chemical which is destructive to micro-organisms. The enlargement which is so commonly seen in disease would then be accounted for by a hypertrophy in response to a sudden demand for additional defences against infection.

This, of course, is purely speculative, and we have, at present, no evidence in support of this. But it is hardly conceivable that an organ of this size can be for no purpose, beyond the contributory hæmopoietic function which it shares with other organs. In spite of the fact that splenectomy is not followed by fatal results, and that after this operation other glands take on the known functions of the spleen, it seems highly probable that the future will disclose some fresh facts about the splenic function, and will prove beyond doubt that it elaborates a hormone which may be included among the internal secretions of digestion.

Splenic extract has been prescribed in a wide variety of cases. Thus, it has been given in typhoid with good results; in splenomegaly, in malaria, also in anæmia, and in morbid states associated with a low blood-count. Some observers speak enthusiastically of its influence in reducing the size of an enlarged spleen, more especially in what we may speak of as "idiopathic" splenomegaly.

The dose of splenic substance varies widely with different authorities, but large doses of the fresh substance are said to be badly tolerated. The dry extracts may be given in doses of a few grains, and as much as 15 grains daily are usually well tolerated. It undoubtedly finds a useful field of activity in exhaustive maladies, and in patients showing signs of a diminished resistance to infection. In the disease just referred to it may confidently be administered, with the object of raising the resistance to the invading organism, assisting metabolism, and thus maintaining the strength of the patient.

This, then, is a brief survey of the internal secretions concerned in digestion, and of their relations to each other. We have attempted also to indicate the lines along which treatment by administration of the extracts of these organs can be carried out, and we have tried to show where such therapy may succeed. As such treatment is still in its infancy, and as there are a good many reasons why it cannot be expected to be successful in every case, this should make us all the more careful to diagnose, so far as lies in our power, the exact causation of every case which we treat with organo-therapy; and we should remember that, while certain of these preparations are toxic, others are not so. As an adjuvant to ordinary methods, the extracts referred to in this chapter should be found very useful.

REFERENCES.

[1] Sweet and Pemberton, Exp. Observ. on "Secretin," quoted in *Practitioner*; H. R. Harrower, Practical Hormone-Therapy.

[2] Harrower, *ibid.*, pp. 64-65.

[3] Langdon Brown, *Practitioner*, vol. xciv., No. 2, p. 252.

[4] L. Williams, The Therapeutic Promise of the Internal Secretions, *Practitioner*, 1911, lxxxvii. 605.

CHAPTER XI

THE INTER-RELATIONSHIP OF THE DUCTLESS GLANDS AND THE NERVOUS SYSTEM

In several parts of this book reference has been made to the mutual relationship existing between the nervous system and the internal secretions. The sympathetic system in particular shows an interaction with the endocrine system, both morphologically and from the physiological standpoint. In this chapter it is proposed to collect the facts bearing upon the interaction of the nervous system and the ductless glands.

We will commence by a brief description of the sympathetic system, in the hope that it will clarify to some extent the difficulties which beset the understanding of this subject. We shall then discuss individual secretions and their relation to nervous control, and conclude with a summary. In the next chapter will be found a description of the endocrine system and nervous disorders, more particularly those known as "shell shock," "traumatic neurasthenia," etc., for they form examples of acute disturbances associated with endocrine manifestations.

The Sympathetic System.

In his work on "The Involuntary Nervous System,"[1] Gaskell describes the sympathetic nervous system, and makes use of three principles which deal with the subdivisions of the sympathetic, their relative action, and the correlation existing between the endocrine glands.

The first principle consists in the recognition of two subdivisions of the sympathetic system: (1) The autonomic, and (2) the sympathetic proper. The autonomic system consists of that portion of the vegetative system "which does not provide centrifugal rami communicantes to the ganglia which lie on the bodies of the spinal column, but is found in close relation with the third, seventh, and ninth cranial nerves, and with the three first sacral nerves."[2] The chain of ganglia receiving the rami communicantes from the spinal cord and the visceral ganglia composes the sympathetic proper.

The next point of importance is that these two portions, both of which innervate the viscera, are antagonistic to each other in regard to the separate functions of those organs.

The second principle concerns the selective action of the endocrine secretions on the two parts of the vegetative system. It has been shown that this selective action is of the first importance in the regulation of the blood-supply of an organ. For example, to take one secretion first, about which there is no doubt, we know that adrenalin acts through the terminations of the true sympathetic; and that it excites the secretions of some organs, while it inhibits others. It is probable that its action upon metabolism in general is due to its stimulating effects upon the liver. Experiments have shown that stimulation of the splanchnic nerve to the liver increases glycogenolysis, and that this only occurs when the adrenals are intact. The work of Elliott has shown that adrenalin has the same action as stimulation of the true sympathetic. As an instance of the inhibitory action of adrenalin, we may refer to its effect upon peristalsis, which is exactly analogous to that of the sympathetic.

The third principle is the recognition of the special correlations existing between these glands. There is, as we have seen in other parts of this book, a mutual action between some secretions, and an antagonistic action between others. One secretion may stimulate into activity the product of another gland, in this sense a "true hormone"; a second, however, may inhibit the secretion of another member of the endocrine group. The adrenal secretion has a stimulating action upon the pituitary and upon the thyroid; either produces a similar action upon the adrenal. All three can inhibit the secretion of the pancreas, and perhaps also that of the parathyroid and thymus glands.

Other assisting and antagonizing actions at once occur to the reader; and in Chapter I. will be found other instances. It is possible, moreover, that the antagonism existing between the two parts of the vegetative nervous system may depend on the various actions of the endocrine glands. It is probable, also, that the tone of the visceral nervous system is maintained and influenced by the secretions of the endocrine glands. It will repay us, therefore, to familiarize ourselves with what is now known about the nervous supply of the visceral organs and the sympathetic system as a whole, and to try and understand how this is linked up, and its action modified by the internal secretions.

Gaskell, whose work on the involuntary nervous system has thrown so much light upon this subject, summarizes the divisions and actions of the sympathetic system in the last chapter of his book.* He divides the unstriped muscles of the vertebrates into certain groups, classified according to their innervation and their response to "certain substances formed naturally in the body." There are six groups in all: five of these respond to very small quantities of adrenalin, while the sixth (the musculature of the endoderm) contracts in the presence of a small quantity of acetyl-choline. "The striking action of these two substances, adrenaline and acetyl-choline, is correlated with the differences in the innervation of these two groups of muscles."†

In explaining the action of these two groups from the embryological standpoint, Gaskell says that investigations show the nerve cells of both were

* "The Involuntary Nervous System," Chapter XII., p. 150 *et seq*. Longmans, Green and Co., 1920.

† *Ibid.*, p. 150.

originally in the central nervous system, but that, in travelling out from it, the sympathetic cells have been accompanied by adrenalin-containing cells, and that these cells form the chromaffin system. Cells of this nature are seen in the leeches, and Gaskell considered that they form the origin of both the sympathetic and chromaffin cells of the vertebrate.

These nerve cells, originating in the central nervous system, include inhibitory and motor cells in both nervous systems (sympathetic and enteral), the inhibitory cells of one system travelling with the motor cells of the other, thus establishing the antagonism, exemplified by such a mechanism as the sphincter.

Turning now to the relation between the nervous and humoral control of metabolism, we have already referred to the work of Eppinger and Hess.* These writers consider that two groups of symptoms may exist, the one dependent upon the cranio-sacral system and called vago-tonia, the other characterized by over-action of the sympathetic part of the vegetative nervous system, and called sympathetico-tonia, or sympathotonia.

It has been noted that disturbances of the autonomic system are associated with disorders such as those seen in the lymphatic diathesis, and in which the thyroid, thymus, and other of the ductless glands, are believed to be implicated. On the other hand, the sympathotonic symptoms are those seen in hyperthyroidism—hyperthermia, restlessness, tachycardia, and atony of

* Chapter III., p. 63.

the stomach and intestines. If, then, this is the underlying pathology of those cases known as Graves' disease, it would be interesting if we could take the investigation one step farther and find out whether this atony, which is a constant feature of this type of case, is dependent upon over-stimulation of the enteral sympathetic system by a chemical manufactured in the body, either one belonging to the normal endocrine group or one resulting, *e.g.*, from the products of intestinal digestion. If we could say, as Gautrelet did, that the action of tissue extracts is due to choline, we might have advanced a step; for we could believe, with him, that the "choline glands" were antagonistic to the "adrenalin glands." But this appears not to be so. Swale Vincent says, "Even if the action of tissue extracts were in reality due to choline, there would be no grounds for such an assumption as is here put forward. The theory that the normal blood-pressure is maintained by a series of antagonistic chemical messages arriving from the different glands and tissues of the body has been put forward previously in different forms, but there is no experimental evidence to support it."[3]

It does appear, however, that not only the vegetative nervous system is controlled and affected by endocrine action, but also the entire nervous system. The changes seen after parathyroidectomy are certainly suggestive of a widespread involvement of the nervous system, and the clinical evidence of the psychophysical condition of cretins before and after they have been furnished with thyroid extract may well support this belief. One observer has put forward the theory that the neuroglia may be included among the hormone-producing glands, and that the secretion of this tissue has widespread influences upon the sensitivity of the nervous system.

The clearest relation which has yet been established between the nervous and the humoral control is that of the true sympathetic and of adrenalin. We know that the action of adrenalin is identical with that produced by stimulation of the sympathetic, and the work of Gaskell has suggested how this has been brought about. He pointed out that in segmented annelids certain nerve-cells in the central nervous system contain adrenalin, and he says that in this class of the vertebrates " we are watching the genesis of the sympathetic nervous system."

The knowledge which the future holds for the student of the internal secretions will be largely built up upon investigations into the action of the vegetative nervous system.

The Relation of Hormones to Nervous Control.

We have seen that embryology shows the intimate relation existing between the chromaffin tissue and the nervous system, and that physiology proves their similarity in action. In this section we shall draw attention to the mutual relations of various hormones and the nervous system.

Asher and von Rodt showed the production of the internal secretion of the thyroid to be under the control of the nervous system. From the other view-point the action of the thyroid secretion upon the central nervous system is very striking, and is well shown in typical instances of hyper- and hypo-thyroidism. The response to stimuli in these two conditions is widely different.

The effect upon metabolism of thyroidectomy is interesting. Large amounts of sugar may be given after removal of the thyroid without the production of glycosuria. This means that the sugar is stored and not mobilized. Adrenalin, as we have already seen, has an action in the mobilizing of sugar, and it is possible that the loss of the thyroid secretion decreases the action of the adrenalin in producing glycosuria. Both the thyroid and the adrenals probably act upon the same mechanism, the thyroid secretion producing its action by stimulating the terminations of the sympathetic in the liver (Paton).

If adrenalin be instilled into the conjunctival sac in patients suffering from hyperthyroidism, dilatation of the pupil is produced, which is an example of the action of adrenalin where the thyroid is in excess. The thyroid exerts its influence upon carbohydrate metabolism mainly through nervous channels. It is probable that the same mechanism is involved when protein metabolism is concerned, because, as Paton says, the close relation existing between sugar formation and protein metabolism is now recognized. The work of Mansfeld, which showed that the increased nitrogen output which usually follows the deprivation of oxygen does not take place after thyroidectomy, "shows how close the association of the thyroid is with protein catabolism."* This association appears to be brought about by the influence of the thyroid upon the liver. In like manner the evidence of physiological experiments is in favour of the view that adrenalin acts upon metabolism through the nerve terminations in the liver. The antagonistic action of ergotoxin and adrenalin in this relation suggests that the action is on nerve-endings.

The nerve and endocrine relations with reference to the parathyroids have already been discussed. The thymus and parathyroids are similar in their action upon the nervous system. Both exercise a depressing effect, which has been attributed to the metabolic changes, more particularly with regard to diminution in the calcium content. Paton rejects both this explanation and that of an acid intoxication which has been put forward to explain the symptoms of tetany; the former because, in dogs dying of tetany, the brains have been found to contain a slightly *greater*, not less, proportion of calcium; the latter because, experimentally, the amount of ammonia required to produce symptoms of acidosis is very large.

The action of the thymus and the parathyroids is probably directly upon the spinal synapses. This is

* "The Regulators of Metabolism," p. 199.

of a depressing nature, and is the opposite of that exercised by the thyroid gland.

Pituitary extract is analogous to adrenalin in its action upon the metabolism of carbohydrates, and probably also by means of nerve-endings in the liver. The question whether it acts upon muscle fibre, upon the neuromuscular function, or upon the nerve-endings, has not been settled.

The gonads must be studied from the two standpoints we adopted in Chapter IX.—namely, their effects upon growth and metabolism and their effects in producing the phenomena of sex. As regards the first, little is known as to how the effects associated with the presence or absence of the gonads in both sexes are brought about. Certainly it cannot be said that there is conclusive evidence that it is by direct action upon the nervous system, although it may be that these effects are brought about by action upon the vasomotor mechanism. The influence which the internal secretion of the gonads exerts upon the sexual characteristics is undoubtedly by means of the nervous system; for the study of animals has shown beyond question that it is by means of nervous reflexes that these characteristics are brought about.*

The pancreas exerts an inhibitory action upon the adrenal secretion, so far as the mobilization of sugar is concerned. Paton thinks it is probable that the pancreatic secretion acts upon the same structures as

* See Chapter IX., p. 202, for an account of the experiments of Steinach.

the adrenals and the thyroid in this relation, but in the opposite direction, inhibiting instead of facilitating. We thus have a common neural basis, stimulated by one set of secretions and inhibited by another. Such a balance is probably often in action in the course of metabolism, or some modification of this mechanism is made use of to bring about the complicated metabolic exchanges.

Summary.

1. The vegetative nervous system is composed of two parts, the autonomic and the sympathetic.

2. These two parts are antagonistic to each other in so far as the functions of the organs are concerned. This is shown by their reaction to drugs—*e.g.*, pilocarpine stimulating the autonomic and adrenalin the sympathetic.

3. The various internal secretions have a selective action upon the two parts of the vegetative system: the pituitary secretion stimulates the autonomic, adrenalin the sympathetic.

4. There is reason to believe that the chromaffin tissue has been evolved from the central nervous system by means of cells which have travelled outwards carrying adrenalin with them. This is additional evidence of the intimate relationship which exists between the involuntary nervous system and the internal secretions.

5. The complex activities of the body, both metabolic and vasomotor, are brought about both by means of

hormones and by nervous influences activating these secretions. In many instances there is experimental evidence to show that the chemical stimulus is the more important, and that it plays a larger part in the regulation of metabolism than does the nervous.

6. The development of a nervous system is a comparatively late event, stimuli being primarily of a chemical nature. This would suggest that the chemical is the dominant factor.

7. The chief if not all the functions, in connection with metabolism, are regulated by two sets of impulses, a stimulatory and an inhibitory. The autonomic and the sympathetic balance each other from the nervous aspect, while the chemical is served by two secretions having opposing actions so far as a particular function is concerned.

References.

[1] W. H. Gaskell, *The Involuntary Nervous System.* (1920.)
[2] R. G. Rows and David Orr, *Functional Mental Illnesses.*
[3] Swale Vincent, *Internal Secretion and the Ductless Glands.*

CHAPTER XII

THE ENDOCRINE GLANDS AND NERVOUS DISORDERS

Introduction.

SINCE the first edition of this book was published, considerable work has been done on the relation between the various endocrine glands and disorders of the nervous system. The interest in this work has been accentuated by the numerous and striking cases of functional disease attributable to the war, many of which present features unlike anything previously met with.

In this chapter the author proposes to discuss the more recent work which has been done on the complicated physico-psychical basis of these disorders; and to consider at some length the part played by the internal secretions.

In a certain proportion of the functional nervous disorders—those, to wit, which have been christened "shell-shock," "shell-concussion," "traumatic neurasthenia," etc.—there are, very frequently, ample evidences that somewhere in the chain of cause and effect there enters the element of the internal secretions. In any large number of such cases, particularly if examined at an early stage, a certain proportion will be found to show symptoms which lead us to suspect undue stimulation of one of these vital chemicals, the internal secretions. Others, cases of longer duration, will develope in the course of weeks or months such definite signs as tachycardia, undue sweating, enlargement of the thyroid, fine tremor and loss of flesh with asthenia. The sympathetico-tonic picture thus displayed is very striking;* and it is often enough encountered among the war psycho-neuroses to make the neurologist on the lookout for such indications. Among a large number of functional neurological patients which the present writer has had the opportunity of observing, both in France and in this country, there were many who displayed one or more of the symptoms named above.

When the effect of adrenal stimulation which follows emotional shock is taken into consideration, it is only to be expected that such symptoms should be observed. Cannon, in his classic work on this subject, showed that the rôle of the adrenals was of prime importance in maintaining nerve-tone; and, further, that one of the effects of adrenal stimulation was increased action of the heart, vasomotor excitability, and other symptoms, which are also seen after psychical stimulation. We shall refer later in greater detail to the bearing this has upon our present study.

* See Chapter III., p. 63, for reference to the type of case which Eppinger and Hess have thus described.

If the adrenals, to take one factor in the endocrine circle, suffer undue stimulation, we now know that the changes resulting are not due solely to the secretion of those glands, but that others are in turn affected. For instance, it has been shown by Osokin* that the adrenals have a definite effect upon the thyroid: for this observer produced marked histological changes in the cells of this gland by repeated injections of adrenin. Moreover, stimulation of the splanchnics appears to produce increased thyroid action.

Here, then, we arrive at a further stage in our initial inquiry. Presuming, in a case of war-shock such as we have just referred to, the emotion is the initial cause, this will produce an increased secretion of adrenalin, which will account for the immediate symptoms, such as are seen at the commencement of the disorder; while those patients who show these symptoms, together with an enlargement of the thyroid, may be regarded as suffering from hyper-adrenalism, which, in turn, has reacted upon the thyroid, producing an enlargement of this organ. Such an hypertrophy may be regarded as analogous to that produced by Osokin in his experimental injections.

It will be noticed that we have assumed a psychical origin in such a case. This is warranted when we consider—

(i.) That Cannon showed that purely sensory stimuli could stimulate glandular secretion.

* *Russk. Cratch*, 1915, xiv. 300 (quoted from Swale Vincent).

(ii.) That in the majority of war neuroses the psychical element has been abundantly proved to play a most important part.

To obtain a clear understanding of the problems of the psycho-neuroses, we must remember that the evidence produced by Cannon is of the greatest importance in explaining the mechanism of these disorders. For he showed not only that nerve-tone was dependent upon the regular secretion of the adrenals, but that the latter secretion was largely determined by the mental content.

Before discussing the physiological facts which recent work has placed at the disposal of the neurologist, it may be as well to glance at the psychological factors which underlie so many of these nervous disturbances.

The Psycho-Neuroses.

In considering these neuroses with reference to the internal secretions, we are faced with an initial difficulty—namely, the ambiguity in the meaning of the term neurasthenia. Neurasthenia may be regarded as a nervous exhaustion in the sense its originator used the word: for Beard, when he referred to neurasthenia, considered that its whole origin was in a lowering of the nervous potential, and in his conception he included the mental exhaustion which Janet subsequently so clearly defined under the term "psychasthenia." Or, again, neurasthenia is sometimes used to denote every symptom which is ever encountered in the psycho-neuroses. Physical exhaustion, "irritable weakness," gastro-intestinal disturbances, mental abnormalities (including the manifestations popularly known as hysteria), phobias, obsessions, tics, tremors, etc., are all included under this term by some writers.

It will be better, perhaps, not to attempt at present any decision between the different meanings of the term neurasthenia, but to let the meaning clear itself in the course of our description of the relation which the endocrine glands bear to functional nervous diseases. We commence, therefore, by a short survey of the psycho-neuroses in general; this will lead us to a definite idea of the syndrome of symptoms included under the various terms: we can then consider the relation each disease bears to the endocrine glands, so far as we are able to discriminate between them.

(a) *Historical.*

Until the latter part of the nineteenth century functional nervous disorders remained, for practical purposes, undifferentiated. The popular conception of "nerves," which remains undefined and undefinable to the present day, held undisputed sway. This may fairly be said to summarize the existing state of neurology until Beard, about the middle of the nineteenth century, introduced the term "neurasthenia." Beard included in this term, as we have already said, all those variegated symptoms which he regarded as due, directly or indirectly, to an organic nervous exhaustion.* At that time no psychogenic conception had arisen to account for any or all these manifestations.

This view was largely held, especially in America, until Charcot put forward the doctrine that hysteria (to take one more or less clear-cut clinical picture) was dependent upon idiogenic causes. He showed clearly that the individual manifestations of this disorder owed their origin to mental workings. Charcot's outlook may be said to have revolutionized the views held at that time in regard to functional neuroses.

The idiogenic conception of hysteria was enlarged upon by Möbius, whose view was that the manifestations of hysteria were due to "representations." This brings us to the work of Janet, whose writings (from 1889 to 1903) have given us three clear-cut pictures into which we can fit the many mental and physical abnormalities which were formally dumped together under the generic name of "nervous exhaustion."

Janet divides the symptoms and signs of the psychoneuroses into three groups, which he calls hysteria, psychasthenia, and neurasthenia. For him, hysteria represents a typical mental disintegration (*dédoublement*) taking the form of what he calls a "molar dissociation."†

* See articles by author, *Practitioner*, April, 1913, and August, 1915, for a description of this conception.

† By "molar dissociation" Janet means a dissociation *en masse*, a splitting of the mental processes, so that two separate and unconnected streams exist in the mind. By this concep-

(b) *Janet's Conceptions.*

In his conception of hysteria, Janet includes such symptoms as anæsthesias, amnesias, somnambulisms, "attacks," etc.; and these he explains as being due to a splitting of the mental processes.

By psychasthenia, Janet indicates cases of psychical instability characterized by a formidable list of symptoms, classified by this author into groups. These groups comprise obsessive ideas and impulses, "forced agitations" (including the anxiety neurosis), feelings of incompleteness, and insufficiencies, whether of psychological or physiological causation. These he ascribes to a loosening of the elements which go to make up the entire personality, and not to a complete cleavage as occurs in hysteria.

Neurasthenia is also retained by Janet, but used to denote those cases characterized primarily by physiological exhaustion (gastro-intestinal atony, undue fatigability, etc.).

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tion, he accounts for the anæsthesias, amnesias, paralyses and contractions, etc., so commonly encountered in this complaint. Such a view goes far towards explaining the apparently anomalous character of functional disorders—*e.g.*, a functional paraplegic who can "walk in his sleep," or the deaf-mute who "blinks" at a loud noise, thus showing that some appreciation of the sound has been conveyed to his mind.

In similar manner, he accounts for the symptoms of psychasthenia, attributing them to a certain dissociation which he calls "molecular"—*i.e.*, *not en masse* (loosening of the personality, *not* an entire cleavage).

Since Janet's time, his theories have been expanded and adapted, but, in particular, his conception of the causes of these dissociations has been replaced to a large extent by the work of Freud, Jung, Adler, and others. These authors have evolved elaborate mechanisms to explain the "dissociations" which are presumed to be at the basis of the psycho-neuroses.

Retaining for the moment the conception of dissociation of mental processes, we naturally ask for some more definite reason for this dissociation than the "sticking together" hypothesis given by Janet. Freud and his followers offer reasons for such dissociations; and these are to be found in the existence of complexes, conflicts, indirect manifestations of repressions, etc. Such mental occurrences as these are the explanations of *why* dissociation occurs; and afford a useful guide in endeavouring to understand the mental mechanisms at the basis of the psycho-neuroses.

(*c*) *Nomenclature.*

It is hoped that this digression will help us to understand some of the difficulties which face us in endeavouring to trace the various links in the chain of cause and effect which constitute the typical case of functional nervous disease. It has been inserted here in an endeavour to crystallize our ideas as to these disorders; so that in any further reference to the subdivisions of the psycho-neuroses in this chapter, the reader may grasp clearly to what particular group of symptoms we are referring.

We are bound to admit that in all these patients the physical and psychical elements are more inextricably blended, and less easily recognizable than in any ordinary disease. Any classification, such as we have just recounted, must perforce be limited in its utility, for it is not, and probably never will be, possible absolutely and arbitrarily to make any complete and final classification of the psycho-neuroses, for the reason that it is equally impossible to divide individuals into absolutely clear-cut temperaments. The most we can do is to lay down rough boundaries, marking off one type—comprising a more or less constant group of symptoms—from others.

By hysteria, then, we mean that group of cases exhibiting the features outlined by Janet. It is characterized by the symptoms we have enumerated.* By psychasthenia, we refer to cases characterized by phobias, hesitations, doubts, anxieties, etc.; while the term neurasthenia will be kept for the cases showing a preponderance of symptoms referable to physical exhaustion—*e.g.*, fatigability, indigestion, disturbances of excretion. This rough-hewn classification will, it is hoped, serve to keep any subsequent remarks about the internal secretions and their relations to these disorders more or less clear.

* The cases referred to by Freud as "conversion" hysteria, form a large part of the war cases of hysteria. By this term is meant those cases in which mental energy is converted from normal to abnormal somatic manifestations.

(*d*) *War Nomenclature.*

Since the war began, many new terms have come into more or less general use to describe the functional nervous disturbances arising from the incidentals of active service. Of these probably "shell-shock" is the most commonly in use. What is meant by this term it is not always easy to say. Presumably its use in the popular mind is to include any functional nervous disturbance occurring under shell-fire without any external injury. Such use obviously would include any condition from what is known in the vernacular to "having the wind up," to a serious lesion such as intra-dural hæmorrhage. Its scientific use is hardly more satisfactory. It definitely includes a condition of concussion, either cerebral or spinal; all functional nervous disorders; and it has even been used to denote a psycho-neurosis arising on home service!

To prevent needless misconception this term should be kept for "the condition which follows exposure to the forces generated by the explosion of powerful shells in the absence of any visible injury to the head or spine. In all cases there is an organic basis, which consists of the more or less evanescent changes in the central nervous system resulting from the concussion caused by aerial compression, to which is often added concussion of the head or spine caused by the sandbags of a falling parapet, or by the patient being blown into the air and falling heavily on to his head or back. On this organic basis hysterical or psychasthenic symptoms are often superposed."*

So much for shell-shock. Where a history of definite trauma is obtainable, it will be found that the term "shell-concussion" is convenient and accurate. In those cases where the explosion has occurred in a confined space, the patient is liable to be rendered unconscious by the effects of carbon monoxide poisoning, as Mott has pointed out.

In many, if not the majority, of cases of functional disorder arising in the firing-zones, some such initial cause as being blown up or buried is ascertainable. A large proportion of these patients do not recover in a relatively short time, as would be expected, were this the only cause, but on the contrary they are often difficult to treat and their cure is notoriously slow. It is justifiable to assume, therefore, that the primary cause has led to the initiation of a cycle of processes, either physical or psychical, or both, and that this causes an enduring abnormality of functioning. In other words, either an hysteria, a psychasthenia, or a disturbance of physical harmony has resulted.

In employing the term "shell-shock," therefore, we shall confine its use to those cases presenting definite signs of cerebral or spinal trauma—the immediate effects being unconsciousness, with stertorous breathing, which may or may not lead to death. If the patient survives, he is left with a variety of symptoms—some of which, at any rate, are directly due to a

* Hurst, *Brit. Med. Journ.*, No. 2961, p. 413.

mental disturbance supervening on the initial shock. Among these are included such various symptoms as partial or complete amnesia, persistent headache, etc. The "battle-dreams," which are so common a feature of these cases, point to a definite mental mechanism, which is best explained by the Freudian theory of repression.*

These cases, therefore, by the time they reach the base hospitals, may be considered as examples of complicated psycho-physical disturbance. Somewhere in the etiological chain is found a disturbed endocrine balance. It may be that the timorous individual has been stimulating his adrenals for a considerable time before he actually comes under fire, thus paving the way for an early breakdown. This would account for those patients who suffer from a psychoneurosis after only a few hours or days in the front line.

The length of time a soldier has served without a breakdown is some slight indication as to the main chain of cause in his condition. A case which breaks down at the first test may be assumed to be composed primarily of psychological factors, unless a definite history is obtainable of actual trauma from an explosion, fall of earth or débris, etc. In the nomenclature here adopted this case would fall into one of

* All experiences painful to the individual are repressed into the unconscious: they are subsequently prevented from reappearing by the "censure"; but this latter is weakened during sleep, enabling the painful experiences to emerge in dreams.

the subdivisions of the psycho-neuroses, according to the particular symptoms present.

It has been noticed and recorded by more than one observer that the wounded who have been blown up, buried, or otherwise exposed to the stresses of the firing-line, show a much smaller percentage of nervous disturbance than the unwounded. In other words, in those men suffering solely from "shell-shock," we are justified in assuming some predisposing factors. Some of these factors we shall outline in a subsequent section.

To recapitulate our nomenclature, therefore, we can divide these cases as follows, utilizing a scheme of the kind given on p. 257.

The term "shell-shock" will, in this way, be confined to a more or less transitory condition, and will pass on to one of the following:

1. Speedy recovery.
2. Definite concussion.
3. The appearance of symptoms of the psycho-neuroses.

In either of the second or third possibilities the patients may develope symptoms which will be lengthy in their duration. This may be assumed to be the most marked difference between the first on the one hand, and the second and third on the other; and it is here submitted that one factor in the determination of such cases is that the disturbance has been transmitted to the endocrine glands. In many instances

SHELL-SHOCK.

- Transitory symptoms clearing up in a few days.
- Concussion.
  - Death.
  - Organic sequelæ.
  - Functional sequelæ.
- Psycho-neurosis.
  - Hysteria.
  - Psychasthenia.
  - Neurasthenia.

Functional sequelæ, Hysteria, Psychasthenia, Neurasthenia.

- Endocrinous disturbance.
  - Hyperadrenalism.
  - Disfunction of Sex Glands.
  - Hyperthyroidism.

Explanatory Note.

Shell-shock may lead to concussion, which in turn may pass on to unconsciousness and death; to organic sequelæ—*e.g.*, hemiplegia, etc.—or it may lead to one of the functional nervous disorders, ensuing an indefinite time later.

On the other hand, it may lead to an immediate psycho-neurosis, one of the three subdivisions already referred to. In the latter case some predisposing causes may be assumed to be present. Both the second and the third subdivisions of shell-shock may lead to a disturbance of the endocrine balance.

this is obviously so, but it is here contended that this probably occurs in many more cases than are recognized as possessing such a factor.

In making this statement, the writer is far from wishing to decry the obvious psychic element, or to attribute the symptoms and their resistance to treatment solely to the physical. The mental conflict which exists in many of the war neuroses is so marked that any observant person cannot fail to see that this at least is one element (the same can with equal truth be said about many civilian cases). But our object is to emphasize the fact that the case does not begin and end there. As an electric current flows from one level to another, so the disturbance of mental harmony flows to the next level via the sympathetic, affecting the adrenals, the thyroid and other endocrine glands. The result is this: that when such a case has persisted for any length of time, it is extremely unlikely that the disorder has remained confined to the primary centre, but has in all probability succeeded in affecting other systems interdependent upon it, producing a psycho-physical disturbance.

This is an important point, and one which is liable to be overlooked; the advocates of psychological causes and treatment confining themselves to methods congenial to themselves, while the opposite school of thought pins its faith on the open-air-free-from-worry-tepid-bath method.

As is often the case, the middle course (if it includes both) is desirable, for the reason just given. In all long-standing cases, it is a moral certainty that the disturbance ought to be attacked from both aspects, as by the time it reaches this stage, it will be a compound of both mind and body.

Psychological Factors.

In this connection, we will confine our attention to the nervous disorders arising in connection with the war, for the reason that they are extraordinarily common at the moment of writing, and much of what is here said about such cases is applicable, with slight adjustments, to the analogous cases met with in civil life.

In attempting to understand the causation of the psycho-neuroses, it is of vast importance to commence by realizing as many of the factors as possible which exert their influence on the psycho-physical harmony. To do this we must glance briefly at the outside influences, and realize how they react on the individual as a whole.

In his excellent work on "Social Psychology," Professor McDougall deals very fully with the instincts. He describes the primary instincts, with their attached emotions; the secondary instincts, and the "pseudo-instincts."* He points out, for instance, that the instinct of flight leads to the emotion of fear; that the instinct of pugnacity is related to the emotion of anger; and that of repulsion to the emotion of disgust.

* "Social Psychology," by W. McDougall, F.R.S. (Methuen.)

In the turmoil of modern warfare, the soldier experiences psychical stimuli which he rarely encounters in civil life. He is constantly facing danger, and is frequently " up against " countless threats to his self-preservation; in other words, his instinct of flight is constantly aroused. But, with the tradition of his kind, the self-respect he possesses, and the help afforded by that deep-rooted force which Mr. Trotter has named the herd instinct,* the corresponding emotion of fear is kept in check.† But the stimulation is transmitted to the physical system. Fear has been shown to produce an increase in the quantity of adrenalin secreted. The physiological object subserved is to afford the organism greater muscular energy, which can be expended in satisfying the demands of the instinct under stimulation—in other words, it enables the individual to take refuge in flight.

* "The Herd Instinct in Peace and War," by W. Trotter. (Fisher Unwin, London.)

† This is not the place to discuss the fascinating theory of "conflict," which attempts to explain the physical symptoms of nervous disorders as resultants of mental conflict between two instincts. In war cases, the instincts most frequently concerned are those of self-preservation and self-respect. We may draw attention in passing to one fact pertinent to our present inquiry—namely, that the individual who is constantly receiving stimuli to a deeply-rooted instinctive disposition, such as that of self-preservation (the results of such stimulation being guided from their normal psychological course by conscious control), will, in turn, pass on such stimulation to physiological mechanisms, with the results we are now studying.

The Psycho-Physiological Mechanism.

Fear, then, may be regarded as leading to definite sequelæ. In like manner, other instinctive processes produce similar bodily manifestations, as reactions of mind on body. Such reactions are biologically useful, and definitely subserve useful purposes—*e.g.*, the preservation of the individual.

We have already seen the close morphological and physiological relations existing between the adrenals and the sympathetic nervous system.* Now, the sympathetic is stimulated by emotion. This stimulation is shared by the adrenals, through their sympathetic supply; and this in turn leads to a flow of adrenalin. This flow is additional to the steady secretion, which has been shown to take place and to exert a continuous tonic influence on the sympathetic.

The additional supply of adrenalin, in company with the sympathetic activity distributed to all the unstriped musculature, enables the organism to put forth an increased amount of energy. This should normally be used in satisfying the instinct under stimulation at the time: in the present instance the fear should be satisfied by flight.

But, to revert for a moment to the case of the soldier, with the resulting emotion held firmly in check by conscious control, some alternative scheme must be utilized, when the normal sequence is, as in

* Chapter XI., p. 232.

the present instance, unavailable. The energy thus created is not utilized; and there then exists a mass of available energy which, if not expended in some other channel, must be dammed up. This is what appears to happen in many cases of war-shock. The patient is restless, on the *qui vive* at every sound, flushes easily, has tachycardia at the slightest exertion—in fact, resembles strikingly the description given in Chapter III. of the patient suffering from Graves' disease.* In other words, his psycho-physical apparatus has been attuned for the biological purpose of sudden action, but this action has not come to pass.

The physiological mechanism which produces this energy is now well understood. The activity of the suprarenal glands, in company with the sympathetic stimulation, enables the individual to perform feats of unusual strength (more particularly under sudden stress) in response to the emotions engendered, as we have already seen, by instinctive reactions. Again, the stimulation of the sympathetic produces splanchnic vaso-constriction, with an increased systemic blood-pressure; there is increased rapidity in the heart-beat; and an increased quantity of sugar becomes converted from the hepatic glycogen by means of the hyper-adrenia, and available for muscular energy.

Sweating, which takes place on exertion, keeps the temperature normal.

At this stage, then, the individual is prepared to

* P. 55 *et seq.*

react to his environment. In the war cases, we repeat, the normal reaction would be one of two courses. Either the soldier would react by evincing anger and thus temporarily increase his military efficiency, or he would utilize his additional energy in flight. In the former case, he is enabled to meet adequately the enormous demands made upon his endurance; in the latter (where flight is resisted), the baulked emotion produces a condition which the psychologists regard as a mental conflict, and the physiologists as an auto-intoxication from perverted hormones.

The plain fact appears to be, however, that the mental conflict is the primary and more fundamental origin in these war cases, leading by a natural reaction to bodily changes, which, if denied an outlet, recoil on the *psyche* and produce a condition which is thus seen to be made up of mental and physical elements.

The emotions thus aroused lead to continued overactivity of the thyroid and suprarenal glands, and the glandular system so stimulated is like a lake overfull which is ever threatening to overflow and work destruction for the want of a normal outlet. Hence we see in many cases of nervous disorders produced by the war, such symptoms as sudden "starts," myoclonic spasms, tremors of all kinds, and restless movements. Again, the mental elements concerned are active in sleep, producing startling panoramas, which again lead to further thyroid and adrenal secretion.*

* This was well shown in a soldier under my care in France. This patient had been rendered unconscious by the explosion

Thus, to a certain extent, the mental and bodily conditions react upon each other, producing a vicious circle of auto-stimulation.

Hyperthyroidism and the Neuroses.

It has already been said that many patients suffering from war neurosis evidence the signs and symptoms of Graves' disease. We have already described these in some detail;* and we will here content ourselves by emphasizing some important points arising in this connection.

From the earliest recorded accounts of this disease, it is quite clear that the symptoms referable to the nervous system were always prominent. From the description in Chapter III. the reader will see that stress was there laid upon this group of symptoms. The difficulty which faces the student of this disease is one which is encountered in almost every sphere of medicine—namely, the question of the origin of the disorder. Is it primarily psychogenic, or are the symptoms secondary to disordered physical functions ?

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of a shell and had been left with a retrograde local amnesia. He had an " electric-like " twitching of the muscles of the right side of the neck and right shoulder, which only disappeared when the blank in his memory was filled in. They recurred, however, after a disturbing dream, but again vanished after treatment directed to the mental content. After each such dream the patient showed evident signs of an increased adrenal secretion, but was finally cured by psycho-therapy, with the abolition of all his symptoms.

* Chapter III., p. 55 *et seq.*

In speaking of the difficulty of deciding this point, the writer of a recent article says:

"This (the work of Cannon) demonstrates how complete is the cycle, and how difficult it is in a given case to ascertain whether the original cause was psychical or material. In no disease is this more evident than in Graves' disease. Here a succession of nervous shocks may excite the adrenals until the thyroid is put into action, and the threshold of its action permanently lowered—with the attendant phenomena of hyperthyroidism. But again the stimulation of the vagus may come from so material a source as a uterine myoma, or other pelvic irritation—as Hertzler pointed out. But the outcome is the same; the thyroid becomes stimulated until its threshold is permanently lowered."*

We have already pointed out that the reasons for regarding many of the war cases as primarily psychogenic are ample: the same would apply to those cases of Graves' disease among soldiers. It is a well-known fact that the syndrome which we have hitherto called "hyperthyroidism" is frequently met with among the cases of functional neuroses which arrive at the base hospitals; and the present writer has no hesitation in saying that if these cases are carefully examined a certain proportion will show a clinical picture not differing in any marked manner from the pre-war Graves' disease. The exophthalmos is not often marked, but the fine tremor, moist skin, tachycardia,

* Editorial, *Endocrinology*, October-December, 1917, p. 402.

prominent thyroid, and mental irritability are all present. The brisk reaction to any emotional excitement, with exaggeration of those features, shows that the mental element is not negligible. Furthermore, anyone who has had any lengthy experience of this class of soldier-patient will agree that his mental outlook is markedly similar to that of the civilian patient with exophthalmic goitre.

It is difficult to say which symptoms owe their origin to the hyperadrenalism and which to the hyperthyroidism; but the blood-pressure of these patients is nearly always above normal. Among these patients, moreover, many will complain mainly of the cardiac discomfort, with the result that not a few reach the hospitals labelled "disordered action of the heart."

Whatever part in the circle these two glands play, their rôle is obviously an important one, and due consideration is necessary in deciding upon the line of treatment to be adopted in such a case. Rest would appear to be essential in the early cases; and Black records the case of a goitre which disappeared entirely when adrenalin chloride solution was given.* Such treatment, however, should be, in the present writer's opinion, entirely secondary to treatment directed to the mental factors, and the rapid improvement in physical symptoms (*i.e.*, tachycardia, sympathetic irritability, etc.) which has followed judicious treatment directed to the mental state in the war

* New York *State Journal of Medicine*, 1917, xvii. 125.

cases, leads him to believe that, in a certain proportion of these cases at any rate, the mental turmoil is the primary factor.

Dementia Præcox.

Any account of the relation between the ductless glands and the neuroses which omitted some mention of this disorder would be incomplete. For the evidence that the endocrine glands fit in somewhere in the chain of cause and effect is very striking.

In order to avoid a lengthy discussion, we will confine ourselves to an attempt to draw the reader's attention to some salient features of this disease which appear to be directly traceable to an upset endocrine balance.

1. The disease is essentially a disease commencing in adolescence; in other words, when the fresh internal secretions make their appearance, and when they are not "assimilated" to the existing system, they are capable of disturbing the normal balance.*

2. The internal secretion of the sex glands introduces at puberty fresh elements into the hormonic system.

3. This additional and vigorous appeal is such that the cerebral neuronic representatives must suffer strains in their endeavour to meet this call with a corresponding vigour of inhibition.

4. An accumulation of affective tension or subconscious emotion, is brought about.

* Many of the following points are quoted from an interesting paper by Dunlop Robertson in the *Journal of Mental Science* for July, 1915, pp. 392 *et seq.*

5. The physiological channel of outlet for subconscious emotion is the sympathetic nervous system.

6. The chromaffin cells, being developmentally closely associated with the sympathetic nerve-cells, will feel the hereditary biological handicap almost, if not quite, as severely as the neuronic.

7. There will therefore be a hypersecretion of adrenalin, which, in excess of the bodily requirements, is a toxin.

In criticizing the above views, it is necessary to remember—

(*a*) That adrenalin acts quickly and for a short period only.

(*b*) That it is quickly oxidized.

Unless the "hereditarily transmitted defective biochemism"* alters this property of adrenalin, it is a little difficult to understand why it produces the features of dementia præcox, which this writer attributes to it, and why it does not produce the thyroid reaction which it does, in, *e.g.*, the war neuroses.

Again, this author believes that the hypersecretion of adrenalin leads to a cerebral anæmia, and there is a good deal of recent evidence to support the view that there are vaso-motor fibres in the brain.† If this is so, there is some reason to believe that a condition of cerebral anæmia might follow the hypersecretion of adrenalin.

In speaking of the emotional symptoms of dementia

* To which Dunlop Robertson refers.

† See an interesting article by Orr and Rows in *Brain*, vol. xli., part i., 1918, entitled "The Interdependence of the Sympathetic and Central Nervous Systems."

præcox Robertson says: " The subterranean lake, then of vagrant and vibrant emotion, gets vent for its excess by welling up on to the physical surface, through the physiological channel of the sympathetic. The stimulant sympathetic finds expression through the functioning of its peripheral end-organs, and of these the chromaffin cells (which accompany the ramifications of the sympathetic, which are so strongly represented in the medulla of the suprarenal capsules, and which are developmentally so closely associated in origin with the sympathetic nerve-cells themselves) are notable and important members. (We believe these chromaffin cells are first recorded as low down in the zoological scale as the amphibia.) One of their specific functions is to secrete adrenalin, which by the suprarenal vein gains the inferior vena cava, and thence, the general blood-stream. . . .

" The access of an additional and continuous psychic stream of stimulation through the sympathetic to its end-organs will upset the cyclic balance, and cause excessive elaboration and secretion of adrenalin as a functional response. The affinitive derivation of these cells to the neuronic will certainly imply their almost as easy susceptibility to the biological handicap as the neuronic cells themselves. . . . Their 'irritability of weakness' being seen in hypersensitiveness to stimulus, as hypersecretion at first, perhaps later on as hyposecretion."*

Swale Vincent,† in discussing an experiment by

* Robertson, *ibid.*, p. 399. † *Ibid.*

Dreyer, Asher, and Tschehoksaroff, says: "The adrenal secretion is under the control of the thoracico-lumbar sympathetic system. They further call attention to the fact that the phenomena of a major emotional condition, in an animal, indicate the dominance of sympathetic impulses. When, for example, a cat becomes frightened, the pupils dilate, the stomach and intestines are inhibited, the heart beats rapidly, the hair of the back and tail stands erect—all signs of nervous discharge along sympathetic paths."

I have quoted at some length from this article because I desired to emphasize the theoretical relation of the internal secretions to a psychosis. Dementia præcox is the most suitable mental disorder to discuss in this relation, as its origin is still in dispute. The theories of its genesis are, broadly, three:*

1. The toxin theory, which maintains that the disease is due to toxins acting on the nervous mechanism, either through the nutrient fluid or through the organs of internal secretion.

2. The "inherently-defective" theory.

3. The psychogenic theory.

Abderhalden believes that this disease owes its origin to a "dysfunction of the sex glands," and the tests carried out by H. Cotton, Corson White, and W. W. Stevenson appear to bear this out. The results of the Abderhalden tests showed—

1. That this test gives certain definite results.

* Langdon, *Amer. Jour. of Insan.*, 1917, April.

2. That these results were practically negative except in dementia præcox and epilepsy.

3. That in the former condition 81 per cent. showed abortive reaction to sex glands, and 3 out of 55 gave abortive reaction to both thyroid and sex glands.*

These experiments certainly support the view that the ductless glands are vitally concerned in the etiology of dementia præcox, and for this reason we have here quoted them.

It is obvious, therefore, that its relation to the neuroses we have been considering is fairly close, in so far as the internal secretions are concerned—that is to say, that some authors—*e.g.*, Dunlop Robertson—lay stress upon the predominant part played by the adrenal secretions; while others emphasize the part played by sex organs. For this reason, and to make our general survey in this chapter more complete, a brief discussion of this disorder was deemed advisable.

Summary.

We will now recapitulate the main points dealt with in this chapter, and briefly suggest some possible lines of treatment.

In any case of functional neurosis, whether it be hysteria, psychasthenia, neurasthenia, or (in soldiers) the sequelæ of "shell-shock," or, again, those borderline cases which may be regarded as dementia præcox, it is important to remember that we have no right

* *Amer. Jour. of Insan.*, January, 1917, p. 472.

to state dogmatically that the disease is solely psychogenic or solely physicogenic. Our knowledge of these disorders is increasing daily, but even now we have insufficient information to warrant us in stating arbitrarily that either origin is the only and exclusive one in a given case.

This being true for the majority of such cases, it is a good working rule to keep in mind that whereas treatment from both view-points can do no harm if kept under careful observation, treatment from one only may very well prove inefficacious. To illustrate this point, I may perhaps quote a case which I have recently been asked to see. The patient was a young soldier, who had returned from France with "shell-shock" some few weeks ago. He informed me that he had always been "rather nervous," but had enjoyed good health previous to joining the Army. He had been in France about five months, the first four of which he had spent behind the line. He had only been in the firing-line a few days when three shells burst near him, and he lost consciousness. From a close inquiry, it appeared that the shells did not explode particularly near him, and certainly he suffered from no actual trauma or gas poisoning. He regained consciousness on reaching the hospital, and from there was eventually invalided home.

When I saw him his condition had lasted nearly two months, and as he well illustrates the combination of psycho-physical elements, I will briefly describe his symptoms. He was twenty-two years of age, rather poorly-nourished, with a high colour and a good head of hair. The pulse was full and rapid (110 per minute), and he complained of palpitation. The skin was soft and moist, and he suffered from undue sweating on any exertion. There was polyuria and frequency of micturition. The thyroid gland was obviously enlarged: and there was a fine tremor of the hands.

In addition to these symptoms this patient suffered from periodic "attacks," which, from the description of his medical officer, were undoubtedly hysterical in character. I did not witness any of these attacks myself.

The clinical picture was interesting and exemplifies well the combination already referred to. This patient "broke down" at practically the first shelling to which he was exposed; and I have little doubt that his timorous soul had been flogging his adrenals for some weeks before he was actually under fire. The experiences he underwent were probably stored and revived in the hysterical "attacks." But the physical signs were strongly suggestive of adrenal and thyroid excess. The combination of mental and physical signs pointed, in my opinion, to the conclusion that the initial step in the development of this neurosis had been mental; the continual fear had led to hyperadrenalism, and when I saw this patient both psychical and physical elements were in full swing.

I refer to the case as typical of numerous war neuroses, and because it is an instance of a disorder showing the combined symptoms. It will be noted that the condition had been in existence for nearly two months when I saw the patient, and consequently the hyperadrenalism had had time to "whip up" the thyroid, with resulting enlargement of the latter.

There is a good deal of divergence of opinion with regard to the treatment of such cases. The broad lines only can be laid down here, and in Chapters XIII. and XIV. will be found a summary of organo-therapy. A few additional remarks may be helpful.

So far as general treatment is concerned, it is a good rule that such patients must on no account be allowed to exert themselves beyond a safe margin, so long as there are any signs of tachycardia, undue sweating, or restlessness. Those cases showing none of these signs, and especially cases of more or less pure hysteria, must on no account be allowed to remain in bed or in any other avoidable way to depart from the routine of everyday life.

We can perhaps best summarize the treatment as follows, but it must be understood that no attempt is here being made to indicate in what cases any particular treatment is indicated.

I.—*General Methods.*

These include such simple but nevertheless important questions as Rest or Exercise, methods of handling the patient, and the general basis on which subsequent treatment can be built. Isolation can be used in suitable cases, and combined with "suggestion" (see next section) is of great help in hysteria. For cases of hyperadrenalism, rest in the early stages is essential, and in all cases associated with rapidity of the heart's action, the return to a normal life of exertion must be graduated.

The neurasthenic, especially the hypochondriacal type, must never be isolated, but must be firmly treated by a due (not exaggerated) attention to the excretory organs, with, so far as it is possible, every encouragement to turn his attention to his environment, which should therefore be made more attractive than his viscera.

II.—*Psycho-Therapy.*

This type of treatment may be divided into three: Suggestion, Persuasion, and Analysis. For the hysterical and psychasthenic patient one or other of these methods holds out the best hope. Such patients invariably benefit from these forms of treatment; and usually if the mental treatment deals with the primary causation, the secondary results will require further treatment.

For such patients most physical treatments should be accompanied by a large dose of suggestion. Electricity, drugs, and diet should all be utilized so as to convey helpful suggestion.

In a condition of obvious psychogenic origin, probably some superficial psycho-analysis may be very helpful at the start. It is, in the writer's opinion and experience, *not* contra-indicated in war cases of this nature, and the patient is far more likely to reach a higher mental level, when the causative mental factors have been dealt with, than he is if treated solely by some indirect method such as rest and fresh air. It must be borne in mind that these patients have had to undergo, certainly in many instances, a mental and physical strain such as human beings have seldom previously been subjected to. Confessions of their troubles is a source of great help to them, and the sympathetic and intelligent explanation of these troubles does more to assist the beginnings of treatment than anything else.

Persuasion may be regarded as the intelligent balancing of one set of ideas by another—*e.g.*, the convincing of a hysterical paraplegic that his muscles are not paralyzed, but only appear so to him.

Suggestion—waking and hypnotic—are both useful in selected cases, and have their field of usefulness in almost every variation of these disorders.

III.—*Physical Therapy.*

Drugs.—The present writer's experience of the psycho-neuroses, both in civil life and among war cases, has led him to the opinion that this branch of therapeutics plays but a subservient part in these cases.

Sedatives and tonics are, of course, indicated in certain conditions. But the routine administration of large doses of bromides, of valerian, or of strychnine and its compounds, has little to recommend it.

Were the trouble a simple one, or one which requires only a little help in the sedative or stimulant line, their use would be justifiable. But this is rarely the case in such disorders as we are discussing; and something more than the empirical use of drugs is indicated.

Electricity, Massage, Physico-therapy.—Such methods as these are of real help in neurasthenia: but should not be ordered where the symptoms are believed to be mainly psychogenic, because they tend to encourage the belief that the condition is organic and therefore (to the patient's mind) serious. Hysteria and psychasthenia, therefore, are not suitable objects for these forms of treatment, or only so when the early stages of treatment by the methods advocated in Class II. have been initiated.

Physico-therapy is of great value in the later stages of treatment in nearly all these cases. Physical re-education, exercises and graduated drill fulfil a most useful purpose in the restoring of tone to the muscular and vascular systems, and indirectly to the jaded nervous system.

In this class of treatment, moreover, we might emphasize the importance of remedying intestinal stasis, with its accompanying toxæmia, if there is any suspicion of its presence. Many of the patients in these groups of disorders show sign of intestinal stasis (constipation, meteorism, etc.), and it is of importance that this should be remedied at the earliest possible moment.

IV.—*Organo-Therapy.*

Although the various internal secretions play an important part in the genesis of these disorders, they have been left to the last in this summary, for their administration has been fully dealt with in the subsequent chapters, and there are only a few points left to be discussed.

On p. 187 we refer to the use of pancreatic extract in counteracting hyperadrenalism. Unfortunately the author has, at present, had insufficient experience of this mode of treatment to speak decidedly of its effects: but, bearing in mind the large number of patients who exhibit signs of this condition, its extended use might be given a trial.

Thyroid-therapy requires no further mention here, as there is nothing to add to what is contained in Chapters V. and XIII.

Pituitary extract has a limited use. For cases in which this extract would be suitable, the reader is referred to Chapter V.

The internal secretions of digestion are of use in these patients mainly where some concurrent disturbance of the functions of digestion are prominent. Their exhibition is as indicated in Chapter X.

For the neurasthenic patient, the extracts of the gonads, either alone or combined with extracts of nervous tissue, are frequently of the greatest help. Many of the preparations referred to in earlier parts of the book will be found to assist the recovery of the debilitated patient, and so quicken the return of strength to the convalescent from a psycho-neurosis.

If the treatment of these cases is roughly divided into three stages—viz., initial, mediate, and convalescent—we can supply and helpfully prescribe such preparations in the third stage, and be fairly confident that they will assist in restoring the strength of the patient.

CHAPTER XIII

THE THERAPEUTIC APPLICATION OF HORMONES

So far we have dealt more with the physiological and pathological aspects of the ductless glands and their secretions than we have with the therapeutic application, while some of the chapters have concerned themselves exclusively with diseases associated with one or other of the ductless glands. In this chapter we propose to summarize the uses to which preparations of these glands can be put in practice; and we shall hope to outline the more commonly used extracts and to give some indications of their utility.

From this latter standpoint, there can be little doubt that the thyroid must first claim our attention; for this, of all the endocrine glands, gives the best results to administration of its extracts—that is to say, administration over a duration of time. In the following chapter some points in the administration of organic products are discussed.

Now, what is the rationale of hormone-therapy, and with what object do we administer these extracts? Harrower epitomizes these questions in his book, and he divides " the availability of hormone action " into four groups. The first is "substitution therapy"—the supplying of a missing hormone whose loss is due to destructive lesions or other cause of absence of the organ; the second is "supplementary therapy"—"the augmentation, directly or reflexly, of a presumed deficiency"; the third is "specific physiological therapy"—the production of a definite physiological influence which is indicated, but which is not due to any change in the normal hormone production; and the fourth is "empirical therapy."[1]

Now, with this distinction emphasized we can commence to study the facts which have to be considered when we propose to administer extracts of the ductless glands.

First of all, we know that, with certain exceptions, these extracts are not toxic, although some of them have to be given in small doses and with great care. Thus, thyroid extract (as we have frequently pointed out) must on no account be given in the doses which are still found in books—that is to say, from 3 to 10 grains as one dose. Its administration should take the form of fractions of a grain, certainly to commence with. We shall go into the details of thyroid administration later. Again, extract of prostate is highly toxic; and if prescribed it is essential that the initial dose should be small, and its reactions carefully watched. Likewise, the extracts of adrenals and pituitary glands require judicious dosage, and cannot be prescribed in a haphazard manner.

On the other hand, the preparations of such organs as the liver, spleen, pancreas, testicle,* ovary, etc., are in no way poisonous, and large doses can be given with comparative safety. In many instances, however, the administration of these latter extracts partakes of empirical therapy, for, frequently, the decision to endeavour to remedy certain symptoms rests more on a supposed deficiency than upon definite signs of inadequacy of a particular gland. Thus, in cases where intestinal stasis appears to be present, it may be assumed that this depends upon a deficiency of one of the alimentary secretions, to remedy which we prescribe a preparation of the gland in question. This, although empirical, has much to recommend it, and is surely preferable to constant dosing with purgatives, accompanied, as such treatment always is, by unpleasant sequelæ.

Another aspect of organo-therapeutic dosage has been defined by Hallion, and concerns itself with the stimulant action of an extract, administered to man or animal, on the organ secreting that extract. "Extracts of an organ exert on the same organ an exciting influence, which lasts for a longer or shorter time. When the organ is insufficient, it is conceivable that this influence augments its action, and, when it is injured, that it favours its restoration." It is here assumed that, so long as a part of a gland remains unaffected, it is possible to regenerate it from the secreting point of view, so that administration of its extract will have more than a temporary influence.

* See footnote to p. 198.

Again, even supposing that the gland is absent or totally destroyed, the administration of its extract will, in some instances—*e.g.*, thyroid—replace the natural secretion.

Still another aspect of the treatment by extracts of the endocrinic glands is what may be termed "antagonistic action." By this we mean the power of neutralizing an excessive secretion of one gland by the exhibition of an extract of another, assumed to be antagonistic. This adjustment of secretions in order to obtain the hormone balance is one of the most important features of organo-therapeutics, and in all probability the future will see its utility widely extended. In the past, as is well known, when Graves' disease was supposed to depend primarily upon an excess of thyroid secretion, treatment by means of adrenal administration was much vaunted, especially by the late Dr. Gibson, who spoke very highly of the results accruing therefrom.

There is also, in addition to the uses already mentioned, the physiological administration of organic extracts. As an example of this method we may cite the obstetrical use of hypophyseal extract to promote uterine contraction, and the prescribing of the same substance to counteract shock. These uses belong to the class referred to by Starling as "acute," only in the therapeutic sense. Starling, by his division of the hormones into acute and chronic, referred to those hormones which under physiological stimulus secrete suddenly an increased amount of a particular hormone—*e.g.*, the pouring into the blood of adrenalin under the stimulus of fright, and the constant supply of thyroid for metabolic purposes, respectively.

It will be seen from this brief survey of the rationale of hormone-therapy that its uses are many, and that its application is logical. It is obvious that at present we are only on the fringe of the possibilities of such treatment, and that the near future will see its development to an immense degree. We do not mean that the empirical and sometimes illogical dosing by organic extracts, or the exhibition of every extract of the human body in the vain hope of "hitting the target somewhere," will be, or, for the matter of that, ought to be, widely developed. What we infer is that, with increased knowledge of the functions of the endocrinic organs and their relations to each other, fresh fields of scientific prescribing will be open for use, and that many of the cases which we now treat with inorganic medicines, in the blind hope that Nature will step in and cure while we are gaining time, will be positively treated by organic extracts, with the almost certain knowledge that definite symptoms will disappear, and that normal features will reappear.

We will now consider the uses to which these extracts may be put in practice, and we will commence with the extract of thyroid.

In a previous chapter we dealt with the methods of prescribing thyroid extract for myxœdema and submyxœdema, and described the dosage. We will deal here with other uses to which this extract can be put, but must say at once that many of these are founded on empirical reasoning.

For some years the nocturnal enuresis from which so many children suffer has been treated with thyroid extract, and, in many instances, with striking success. Not all these cases, it is needless to say, suffer from thyroid inadequacy, but many of them doubtless do so suffer, and the increased thyroid content of the blood effectually helps to check this enuresis. As Hertoghe has pointed out, a condition of thyroid deficiency nearly always produces frequency of micturition, owing to the poor nutrition of the walls of the bladder, which, in consequence, desquamate rapidly, rendering the bladder unduly sensitive to stimuli. In such cases thyroid extract is urgently needed; and unless it is supplied in increasing doses from within, or the internal supply augmented from without, it is difficult to see how the symptoms arising therefrom can be remedied.

This, then, is one of the uses to which this extract can be put, and another use is connected with this, inasmuch as the condition is frequently found associated with enuresis, obviously because the causation is identical. We refer to adenoids and enlarged tonsils. Hertoghe has rendered an inestimable service to medicine by explaining the underlying pathology of these cases. He emphasizes the induration and thickening which is always present where the thyroid secretion is deficient; not only in the subcutaneous tissue, but in places where formerly its existence had scarcely been suspected. Thus, the tinnitus aurium and deafness of subthyroidics may be assumed to be due to infiltration of the aural passages and apparatus; the growth of adenoids to the same cause; the headaches and nervous symptoms to neural infiltration; and the enlargements of the tonsils to fibrous hyperplasia.

These, which are only a few examples, will serve to indicate the lines along which thyroid-therapy can be conducted. If, therefore, a child exhibits one or more of these symptoms, confirmatory evidence should be looked for. The subject of nocturnal enuresis may show the presence of adenoids, may have enlarged tonsils, or exhibit other signs of thyroid deficiency. The "adenoid facies"—*i.e.*, the mental condition plus the physical conformation of countenance—would be much more correctly described as the "subthyroidic facies." This being so, it will be obvious that such a child owes urinary symptoms of this nature to deficiency of thyroid, and not to local conditions *per se;* but we must emphasize in passing the importance of excluding certain local factors, such as calculus and phimosis. Fascinating as this form of treatment is, and almost limitless as the vista of healing is which is opened by its conception, diagnosis must always precede treatment.

For these patients a small dose of thyroid, increased gradually as is required, is indicated. The initial dose should be a fraction of a grain, according to the age of the patient. Thus, one-sixth to one-quarter of the dry extract or a minim or two of the liquor thyroidei is enough to commence with, and a careful watch is essential to ascertain the reaction of the system to the extract.

Again, obese patients should be examined for signs of thyroid inadequacy, as where such increase in weight is of recent occurrence the treatment should immediately be instituted—the sooner the better—once the diagnosis has been made. Even if the signs of thyroid deficiency are of long duration, the prognosis is equally, or almost equally, good; for although the treatment must be spread over a much longer time, nevertheless the benefit accruing is usually great.

Some of these cases are not solely due to thyroid inadequacy, but are a mixture of thyroid and pituitary deficiency. It is a little difficult to describe the diagnostic features in a few words, but the indications of thyroid inadequacy are a slow pulse, dry and rough skin, subnormal temperature, and obesity; while the signs of hypophyseal deficiency are an increase in weight, a *smooth* skin—as opposed to the rough skin of submyxœdema—a low blood-pressure, and a disturbance of function, as exemplified by constipation, with often a marked degree of meteorism and faulty digestion.

For such cases thyroid should be prescribed, and when the dose has reached what may be regarded as sufficient for the individual case, but still symptoms remain which do not improve, then pituitary extract may be added to the thyroid. Such a procedure will often help where thyroid by itself fails; and, provided the dose of both substances is regulated to the individual case and not by rule of thumb, no ill results should accrue.

If, in patients of this type, no benefit results from the combination of thyroid and pituitary extract, it will often be found that the addition of a small dose of extract of the gonads will be of great help. This is not "a shot in the dark," neither is it trying every hormone in turn; but, in the present writer's experience, cases of this nature frequently respond to a combined extract when they fail to improve on one product. This is presumably because, whatever the original glandular defect has been, disturbances of the endocrine balance have been established by the time the patient comes under notice.

We shall not discuss this subject at greater length here, but further reference to it will be found in Chapter IX.

The preparations of thyroid which may be utilized have already been mentioned, but in order that this chapter may be helpful in actual practice, we will enumerate them once more.

The total extract of thyroid may be given, or the dry extract chosen, if preferred; one part of the dry extract is approximately equivalent to five parts of the other extract. The dose of extracts should be minimal to commence with, and opinions vary as to the margin of safety. So far as the experience of the present writer is concerned, one-half to one grain of the total extract three times a day is a good dose to commence with, and can be increased with due observance of the alteration in weight, pulse-rate, and blood-pressure. Again, if a liquid preparation be preferred, liquor thyroidei, in doses of from a few minims to about seven or eight, is a satisfactory method of administering this extract, provided that the preparation be fresh. Elixir Colloid (Squire) presents this gland in a palatable form, and it can be combined with a pituitary extract if desired. The same firm manufactures a liquid preparation of the pituitary gland, under the name of Elixir Hypophysis Cerebri, with a dose which may range from a few minims to two drachms. These preparations are a convenient way to administer the thyroid and pituitary glands to the same patient at the same time, and the relative doses may be regulated with ease.

The hypophysis may be given in tablets, and several firms manufacture this extract either by itself or in conjunction with other extracts. Or, again, capsules of this gland are put up, either as single products or in combination with other organic extracts, by the British Organo-therapy Company. These preparations are coated in soluble gelatine, air-tight covers, and are thus, it is claimed, less liable to deterioration. This firm manufactures capsules of the whole pituitary gland, or of the anterior lobe only. Injections of the posterior lobe of the pituitary are manufactured by this firm, conveyed in physiological salt solution. We are not so much concerned here with the urgent use of these extracts, as exemplified by their utilization in shock, obstetrical emergencies, and surgical cases, and we shall therefore pass over the employment of adrenalin, pituitarin, and other preparations of these glands for their immediate action, and deal with their use from the routine standpoint only.

The extract of the adrenal gland has definite and powerful properties, and, if used, requires great care in its administration. As it raises the blood-pressure and causes a rapid rise in the pulse-rate, it should never be given in cases of arterio-sclerosis, or in hyperpiesis where there has been hæmoptysis, or in glycosuria. In fact, its prolonged administration is not desirable, except with great care, and, considering that extract of the pituitary is much less toxic, and that the results are almost as favourable, the administration of adrenal extract has not become popular.

There are, however, certain patients in whom the indications for adrenal therapy are plain. To take one example, the case of chronic exhaustion, the patient who is always tired, who complains of muscular tremors upon the slightest exertion, is, I think most clinicians will agree, a most difficult therapeutic problem. While the etiology of such a condition is often obscure, it may well be that adrenal exhaustion is the cause of the present symptoms. Examination will reveal a low blood-pressure at one time, a normal reading at the next. But the ready fatigability is beyond dispute, and is certainly not always psychogenic.

I have utilized adrenal extracts for this condition, both orally and by the hypodermic or intramuscular method.* Their employment requires care, as we have said, and small doses should be administered to commence with, and gradually increased until a full dose is reached. The contra-indications have already been discussed.

Extracts of the gonads, which are sometimes manufactured in combination with extracts of the central nervous system, will be found to have a wide applicability. Thus, in neurasthenic cases, in patients who are run down, and in delayed convalescence, they are frequently of the greatest use. As Brown-Séquard was the first to show with reference to testicular extract, they increase the capacity for muscular work, revive the tired nervous system, and have a general " tonic " influence upon the functions. The present writer has utilized them for several different types of disease (or perhaps the word " disorder " is more suitable), such cases ranging from marasmic wasting to impotence. It is a little difficult to give definite indications for their use, and perhaps it will be better to cite one or more cases in which their use at the hands of the present writer has been attended with success. One was a man aged thirty, with rapid wasting and low blood-

* See Chapter VII., p. 168, for note on the rectal administration of adrenalin. Also see section, p. 162, for discussion on hypo-adrenia.

pressure, who had been in a very depressed mental condition for over two years. His treatment consisted, *inter alia*, in rest in bed for six weeks, with hyper-alimentation and this form of organo-therapeutic treatment. At the end of a month his weight had increased by over one stone, and his improvement in every way was most striking. By the end of six weeks there was a continuance of this improvement, and when he left the nursing home his weight had increased by a total of two and a half stone, his mentality was, for all intents and purposes, normal, and his physical health quite restored.

Another instance of the same treatment was in a man of middle age, prematurely old, with impotence, neurasthenia, hypopiesis, and depression. One month's treatment by these methods restored him to normal, raised his blood-pressure, and restored his nervous functioning. In this case, moreover, there was a flabby condition of the genitals, a loss of sexual power, and a diminution of testicular sensation.

A preparation called "spermin," isolated by Von Poehl, and believed to benefit a number of conditions, most of which emanate from auto-intoxication, has been tried with some success. It has also been suggested that extracts of the gonads are useful in raising the resistance of the body to infection; there can be little doubt that they are valuable in "revivifying" the overworked organism.

In dealing with the hormones which may be supplied from animals, we must refer to those emanating from the alimentary canal and the abdominal organs. Thus, we encounter "secretin," which was isolated by Starling from the duodenal mucous membrane. In normal health this substance is set free from this mucous membrane as soon as the acid chyme enters the bowel. It is difficult to prescribe, for it appears to be destroyed when given by the mouth. Nevertheless, there have been some good results published, notably by Harrower, and this should encourage its further trial. As this hormone is a direct stimulant to the pancreatic juice, its absence or diminution must be attended with some degree of deficient metabolism. A manufacturer's preparation known as "secretogen" is on the market, and the present writer has employed this with some benefit.

Again, Zuelzer, experimenting to ascertain some substance which would have a decided action in increasing peristalsis, discovered a hormone, prepared from the gastric and duodenal mucous membrane, which showed this property. He considers that this hormone is produced in the stomach and duodenum, carried off in the blood, and stored in the spleen. A preparation known as "hormonal" was then manufactured, mainly from the spleen of animals, and administered with or without pituitarin. Apart from cases of spastic constipation and the like, this is, as Harrower points out, a useful remedy for deficient peristalsis.

As there was some danger from the use of hormonal, which was apparently due to the presence of an albumose, this remedy has now been discontinued, and a fresh substance, with the harmful constituent removed, has been placed on the market, and the results quoted in Harrower's book speak very highly of its action, more especially in cases of intestinal paresis.*

Another combination of an internal secretion with the external secretion is to be found in "trypsogen," which contains the pancreatic secretion and ferments. This is recommended for use in cases of diabetes, or where it may be presumed that the pancreas is at fault. Another use for the same preparation is in hypertension, but there are other methods of treating this condition, which must only receive organo-therapeutic treatment of any kind when its origin has been determined.

We will pass over the administration of bile-salts as a rational laxative, as the subject is too large to admit of adequate treatment in a chapter of this length. Suffice it to say here that bile-salts are clearly indicated in some cases of constipation, more particularly where there is reason to suspect a disordered liver, with deranged bile secretion into the bowel. A few grains of bile-salts, about three to five, form an excellent laxative, while in larger doses such an extract is cathartic.

Before concluding this rapid survey of hormonic preparations, we must refer to the less definite internal secretions and their administration. Of these, ovarian extract, either whole extract or else extract of the

* This preparation has received the name "neo-hormonal."

corpus luteum, has been given in a variety of conditions, either alone or with one of the other endocrine preparations. It has been found useful in disorders of the catamenia, at the climacteric, for post-operative disorders, such as those which follow double oöphorectomy, and as an antagonist to certain of the other internal secretions. In similar manner, the extract of the mammary gland finds a field of utility, and has been prescribed for uterine conditions (it will be remembered that there is a close connection between the uterus and the mammæ) and as a galactogogue. Some observers speak highly of its efficacy in this connection.

We have already mentioned the use of prostatic extract, and stated that it is a toxic substance, and therefore of limited utility. The present writer has had insufficient experience of this extract to speak definitely; but it is stated to be useful in controlling the peculiar melancholic condition which sometimes supervenes after removal of the prostate.

General Survey of Organo-Therapy.

We will now briefly recapitulate what we have said with reference to the uses of organic extracts in medicine, and amplify our remarks by quoting some typical cases in which its administration has proved beneficial. As we have arranged this book so that a brief summary of treatment will be found at the end of each chapter, it may be convenient to summarize our conclusions in one chapter, so that, if desired, the therapeutics dealt with in this volume may be gleaned from a perusal of this chapter.

Organo-therapy holds out the hope that it will ameliorate the unhappy lot of many patients suffering from diseases which have hitherto been intractable to most forms of treatment. It has been welcomed with open arms; its component extracts have been prescribed in many maladies, and the reports as to the results of this medication have been various and frequently contradictory. So far as the lesser-known organic preparations are concerned, this book has not had the requisite space to deal with them; neither do they seem, if we may say so, to come within the scope of a work such as this.

The author has endeavoured to describe the grosser lesions in which organic preparations may be employed with a prospect of success, and he has attempted to outline morbid conditions in which such extracts can be prescribed. It must be remembered that an organic preparation may be used in several ways; thus, it may be given to replace the same secretion, which is assumed to be deficient (substitution therapy); it may be administered to increase a secretion which is presumably not supplied by the gland in sufficient quantity; it may be prescribed in the hope of antagonizing the excessive secretion of one or more of the other internal secretory glands; or it may be given purely for its physiological action.

A vast range of utility is thus opened for preparations of the organic extracts; and now that the signs and symptoms of deranged secretion are more widely known, the application of the theoretical knowledge of the endocrine glands to actual therapeutic practice is becoming easier than when such prescribing was almost solely empirical. As an example, the many different abnormalities which thyroid extract will correct, in one or other of its applications, are daily receiving additions, as we discover fresh symptoms of thyroid insufficiency.

Originally its therapeutic use was confined to the treatment of myxœdema. When this disease was seen to be remedied by thyroid feeding, a mild type of the same disease was recognized as yielding to the persuasive powers of this extract. Submyxœdema as a clinical entity has been supplemented by a variety of symptoms, any one of which, when present, may sometimes be ascribed to hypothyroidism. Thus, we may say that a consistently slow pulse points to a deficiency in the thyroid output, although other symptoms must necessarily be present before we can diagnose "submyxœdema." But it does not follow, of course, that every person with a slow pulse has hypothyroidism, although, by the physiological use of this extract, it might be justifiable to accelerate this slow pulse-rate, were it desirable, by the judicious administration of thyroid.

Again, any of the symptoms which are so well recognized when grouped together in the same patient, as pointing to the thyroid as the organ at fault, may be treated by means of this extract, provided that a careful watch is kept of the reaction of the patient to this remedy.

A few examples will explain how this principle may be applied to practice.

Case 1.—M. W., *æt.* 33, married, with one child. Shortly after she became pregnant (three years before the date she first consulted me), she noticed she was feeling better in her general health than she had done for some years, as she had previously suffered from indigestion and constipation, and her "nerves had been bad." She informed me that shortly after her child was born she relapsed, and that about this time brown patches appeared upon her face. These had continued ever since, and her health had never been restored to normal.

On examination, very marked patches of a light brown colour were seen on the forehead and around the mouth. These were so marked as to cover nearly the whole forehead, although there were clear areas of normal skin between. Her pulse was slow, although not markedly so, and the thyroid gland was prominent, the neck measuring 13½ inches at the level of this gland. She was quite abnormally sleepy, and became unduly tired.

I prescribed one half-grain tablet of thyroid gland daily, to be increased in a week to one grain in the day. This was gradually increased until she was taking three one-grain tablets daily.

The result was most gratifying. Three months from the commencement of treatment the patches had almost disappeared, and small areas only of slightly darker colour than the surrounding skin could be seen in a good light. She stated that her general health was much better, and she remarked that "she felt fitter than she had since her baby was born." The thyroid had decreased in size, and the neck measurement was barely 13 inches.

Note.—This case is instructive for the following reasons:

1. The thyroid secretion had evidently increased during pregnancy, when she experienced better health, but had diminished after parturition, which is often the case.

2. The patches of pigmentation yielded promptly to the ingestion of thyroid.

3. The general health improved *pari passu*, both the digestion and the bowels functioning more normally.

4. The decrease in the thyroid gland under this treatment pointed to the swelling as a hypertrophy of the gland, an effort to increase the deficient secretion.

Case 2.—J. W., *æt.* 47, complained of an increasing weight, accompanied by dyspnœa on exertion, broken sleep, digestive disturbances, and constipation. This condition had been of gradual onset, but had been rapidly increasing of late.

On examination, the increase of weight was largely accounted for by deposits of fat in the regions of the abdomen and shoulders; the pulse was about 70, the temperature subnormal, the blood-pressure was 145 mm. Hg, and the urine contained large quantities of phosphates. The skin was dry and rather rough, and the patient most markedly bald; this latter feature he had treated by the adoption of a wig.

I restricted his carbohydrate food, ordered an occasional saline, and commenced with small doses of thyroid. In a month's time he had lost 9 pounds, and felt and looked better. His digestion improved, his sleep became more normal, and his energy returned. This is a year ago, and he still remains in good health, although a relapse in weight occasioned a fresh course of thyroid medication.

Case 3.—An analogous instance is the case of Dr. A. This gentleman consulted me for similar symptoms, but certain points in his case were different. Thus, his inertia was greater, fatigue on exertion was most marked, his blood-pressure was lower, and his general syndrome seemed to me to point to a pluriglandular deficiency.

He took, at my suggestion, small doses of thyroid combined with dry extract of the adrenals. He improved markedly, but had to continue the medication at intervals in order to avoid a recurrence of the symptoms.

Note.—Both the above instances presented neurasthenoid symptoms, but the improvement in each case will afford evidence that many so-called "neurasthenics" are in reality sufferers from a disturbed hormone balance, and in consequence may be helped by this form of treatment.*

Case 4.—M. P., *æt.* 34, complained of undue fatigue, of feeling very unwell each morning on waking, and of a "quite extraordinary tendency to fatigue." He informed me that he had "always had a very slow pulse, as his father had before him." This was certainly true, as his pulse-rate at the first consultation was about 50 per minute. His blood-pressure was low, his temperature subnormal, but his weight was about normal for his height.

There is little further need to discuss this case, for the diagnosis was obvious. His symptoms all yielded to the administration of thyroid extract, which increased appetite, regulated sleep, and approximated the pulse-rate to normal, so that his circulation improved and he was able to resume his normal life, which entailed a considerable amount of active exercise.

Case 5.—An interesting case came under my notice some time ago. A young girl was brought to me whose mental development was deficient, although physically she was quite normal, with the exception of a markedly protuberant abdomen. In this case, as growth proceeded, she had exhibited signs of a lack of mental development, and an eminent surgeon had decided to operate, and implant a thyroid graft in the hope that the thyroid secretion would replace the hypothyroidism which was assumed to exist.

When I saw this patient it was five years since the

* For further remarks on the psycho-neuroses see Chapter XII.

operation, and the main features of the case were as follows:

Her stature was decidedly above the average, and her weight over 12 stone. She was fully developed physically, but her circulation was so poor that she suffered from chilblains on the hands, feet, and legs. Her pulse was slow, about 48 per minute, her temperature markedly subnormal, her blood-pressure low, but there was nothing abnormal in the heart. In the epigastrium and umbilical regions was a large swelling, tympanitic on percussion, which displaced the liver, and cardiac dulness upwards. An X-ray examination in conjunction with a bismuth meal had failed to locate this. The skin was harsh, dry, and scaly. The bowels were regulated by means of liquid paraffin. This case appeared to be due to thyroid deficiency, but it will readily appear that this was not the only secretion at fault. The patient's father came of a family of giants, and it seemed probable that there was an element of *dyspituitarism* in this case; that is to say, that the patient may have suffered during childhood from a condition of unbalanced pituitary action which had been followed during adolescence by hypopituitarism.

Acting upon this presumption, I prescribed a mixture containing a small dose of thyroid extract and a large dose of pituitary. The improvement has been marked, particularly as regards the circulation, but enough time has not elapsed to enable a definite result to be recorded. The abdominal condition is slowly improving, and the tympanitic mass is responding to the stimulation of the alimentary canal by the hypophyseal extract. This swelling I assumed to be a dilated transverse colon which was consequent upon the deficient innervation of the bowel.

Case 6.—W. P., a case of advanced neurasthenia with marked loss of weight. This patient suffered from mental depression and digestive atony, and accompanying neurasthenic symptoms.

There was also evidence of a lowered blood-pressure and a sluggish cardiac action. Although this patient had been under treatment for some time by many different methods, no improvement had taken place. However, a short course of treatment by a pluriglandular preparation was followed by a disappearance of nearly all the abnormalities, and the patient returned to his home and resumed his normal life, which he had been unable to do for three years previously.

Dr. Gowing-Middleton, of Wymondham, has sent me the results of organo-therapeutic treatment in several of his patients. From his most instructive account, I select the following cases.

The first is a case of melancholia, occurring in a woman aged fifty at the menopause. This patient suffered from post-partum melancholia sixteen years ago, and was then under treatment for about two years. The family history is a bad one: the whole of her family being "neurotic," and the patient's mother suffering from senile dementia.

This attack commenced rather suddenly, *at the time the catamenia should have occurred.* The patient appeared dazed, and did not recognize her own son. The change in the mental outlook was very great and very pitiful, as previously she had been a clever and charming woman. From this, she became restless and suspicious, refused food, could not be made to sleep, and consequently was unable to be left alone. Her pulse was extremely soft, but the blood-pressure was unable to be taken, owing to her mental condition.

"Her family decided that she must be placed under certificate. In the meantime I controlled the restlessness by bromides and valerian. But, having read your book carefully, I decided that the best chance of doing anything for this patient lay in prescribing thyroid or pluriglandular extracts. I therefore decided to delay the removal of this patient to an asylum and initiate organo-therapeutic treatment. I gave her hormotone, one tablet three times a day. . . . In ten days the patient had greatly improved. She recognized her children, but was still very suspicious, and imagined that someone was plotting to take the children from her. She, however, began to eat better, the sleep improved, and she gave less trouble. I now . . . increased the hormotone to four tablets daily. In a month she had so much improved that the question of placing her under care was quite settled, for it was no longer needful."

The last reports of this patient state that she is "wonderfully better."

Another case of interest is sent me by Dr. Gowing-Middleton. The patient was a boy, aged seven, an obvious cretin, with symptoms of nocturnal enuresis, obstinate constipation, mouth-dribbling, and "the vacant stare of imbecility." Both testes were undescended, and the abdomen rather large, but no other signs of disease beyond the curious mental condition. The treatment adopted in this case consisted of a tablet containing 5 grains of thymus gland, thrice daily, with half a tablet of hormotone.

In ten days the nocturnal enuresis had quite ceased, and he was able to sleep ten hours without urinating, a feat he had never previously accomplished. The thymus extract was increased to four tablets daily. After five weeks of such treatment, the improvement in the urination had continued, *both testes were in the scrotum*, but the constipation was still troublesome. The mental condition had also distinctly improved.

One other case is instructive. The patient was a young lady, suffering from abdominal pains of great severity, which had been attributed to ovarian neuralgia, and for which she had undergone an operation.

After some years, during which the abdominal pain and constipation continued, her mental condition became unsatisfactory, and she developed depression, amounting almost to melancholia, and became quite unable to undergo even the slightest exertion.

At this stage, when practically all other remedies had failed, she was treated by secretogen. After about a month's treatment her general condition had very markedly improved, she could eat articles of food which she had previously been unable to, and her mental condition approximated to normal. "At the end of seven months her condition is most satisfactory. She has gained in weight, has a splendid appetite, the action of the bowels is much improved, she does not complain about her uterine trouble, and her pains have largely disappeared."

* * * * *

The above cases are certainly interesting and convincing. In none of them can it be fairly said that we are relying upon the *post hoc ergo propter hoc* fallacy to claim a cure. For, in all three, the facts of the cases appear to show that until the new remedy was exhibited, and a fresh weight thrown into one side of the scales, the abnormal conditions present were running their allotted course.

In the first case, time alone will show whether the cure is permanent, or if a fresh exacerbation of the symptoms will arise. Dr. Middleton's second case is a pleasing example of how directly and speedily thyroid extract will revolutionize the psycho-physical apparatus in juvenile myxœdema. His third case is a good example of the help which organo-therapy will sometimes render when all other remedies have failed. From this standpoint it is an instructive case, and one which should direct our attention to other and similar instances of chronic illness, where help may be obtained from the judicious use of these extracts.

The cases we have described will show the lines upon which treatment by the more important organic extracts may be regulated. The legitimate uses to which thyroid extracts may be put are not confined to myxœdema, or even definite submyxœdema; there are a number of symptoms, sometimes isolated, which may be remedied by this substance. Case 1, p. 298, will show that one symptom will often point the way to the underlying pathology.

But, as was seen in Cases 3 and 5, the full benefit was derived by a combination of extracts—in the former by the association of thyroid and suprarenal extracts, in the latter by that of thyroid and pituitary. It is not always easy to decide on the particular combination to employ, neither can definite reasons always be given for the choice. But if the signs which accompany one abnormality appear to be contradictory, either the preliminary diagnosis may be at fault, or else more than the one gland may be at the root of the trouble. As an example, thyroid deficiency produces a harsh, dry skin, hypopituitarism a smooth one. Again, the condition of the hair would lend assistance, as it is scanty and "lifeless" in submyxœdema, but, so far as the head is concerned, is usually the reverse in deficiency of the pituitary secretion.

Again, where thyroid deficiency is associated with hypopiesis and loss of flesh, with languor and undue fatigue, adrenal extract may wisely be combined with thyroid. Such treatment will frequently afford relief in this type of patient, who is very commonly encountered in practice.

There are on the market many pluriglandular preparations, and to these we have already referred. It is scarcely necessary to say that they should only be given where the prescriber knows the exact dose in each tablet or solution; for, if he is in ignorance of the composition and proportion of the constituents, he may well be unable to account for any untoward symptoms which arise. It is probable that the improvement which follows the employment of a pluriglandular preparation is sometimes due to the stimulating effect it has upon the endocrine glands as a whole. Thus, cases of acromegaly have been reported as cured, or much relieved, by preparations containing the extracts of the thyroid, sexual glands, spinal cord, etc., presumably by the restoration of the hormonic balance produced by the antagonistic extracts.

And now a few words to summarize the utility of the more important organic extracts. We will turn our attention first to the thymus gland.

Extracts of this gland have been used in a variety of diseases, ranging from exophthalmic goitre to deficient development. Some observers speak well of its employment in simple as well as exophthalmic goitre, in chlorosis, in rickets, in delayed union of fractures, in rheumatoid arthritis, and in deficient growth. One fact stands out pre-eminently from the mass of supposition in relation to this gland and its functions, and that is that it undoubtedly plays an important part in the calcium metabolism of the body.

It is generally admitted that this gland atrophies about puberty, except in exceptional cases—in fact, there appears to be an antagonism existing between the thymus and the sexual organs.* Ovariotomy is followed by thymus hypertrophy, and the removal of the thymus in some animals produces rapid development of the sexual organs.†

Several authorities also report the changes in the skeleton which have followed experimental thymectomy, and these consist in deprivation of the calcium of the bones, resulting in spontaneous fractures, osteomalacia, and other abnormalities.

It would seem, therefore, that the thymus is concerned with the regulation of the lime-salts in the body, and it is mainly upon this assumption that its extract has been administered to patients suffering from exophthalmic goitre. In this disease the calcium metabolism is defective, and many authorities maintain that the administration of calcium salts should form part of the treatment in every instance. Likewise, the prescribing of extract of thymus might help in this direction, for it evidently exerts a favourable influence in rickets, where the lime-salts are deficient in quantity. It is usually prescribed in doses ranging from a few grains to half a drachm daily.

We have already discussed the uses of parathyroid extract, but perhaps we may here recapitulate the

* In the cretin, described by Dr. Middleton, it will be noted that the testes descended while the patient was undergoing thymus administration.

† See article by Noël Paton, "The Relation of the Thymus to the Sexual Organs," *Journ. Physiol.*, 1905, xxxii. 28.

subject. It has been assumed that these small glands regulate in part the supply of calcium to the cells of the body, and that it is the withdrawal of the calcium which produces the tetany following experimental parathyroidectomy. On this assumption, the extract has been prescribed in a variety of diseases, notably Graves' disease, paralysis agitans, and epilepsy. The dose is small—a fraction of a grain of the dry extract—and should be given once or twice daily. We have already referred* to a most interesting case, reported by Hurst, in which definite parathyroid insufficiency was cured by the administration of parathyroid extract.

In conclusion, let us briefly enumerate the organic extracts which are at the disposal of the practitioner, and their approximate doses. It must be understood that the doses are only approximate, and that no attempt is made to give an exhaustive list, only the more important of the extracts being mentioned.

Thyroid.—The preparations are the dry and the liquid extracts, the dose of the former being from ½ to 1 grain for an initial dose; of the latter 2 or 3 minims. Many products are upon the market in the form of elixirs, capsules, and tablets, either alone or in combination with other organic extracts.

Pituitary.—Two classes of pituitary preparations are in use, one manufactured from a part of the hypophysis (usually the pars posterior), the other from the entire gland. The preparations of the posterior part of the gland are more commonly prescribed, and the dose

* Chapter II., p. 47.

ranges from 1 to 5 grains of the entire extract. The dose of the liquid hypophyseal extracts ranges from 8 to 15 minims, which may be repeated at frequent intervals. A preparation named *Pitglandin*, manufactured from the anterior lobe of the pituitary gland, is supplied by the British Organo-therapy Company.

Adrenals.—As we have already said, the extract of these glands is more toxic than that of the pituitary. The liquid preparation may be prescribed in the form of adrenalin, the dose being from 5 minims to ½ drachm of 1 in 1,000 solution. This preparation may be administered hypodermically. The dry extract may be given in doses of 1 to 3 grains.

Pancreas.—The average dose of preparations of the pancreas is 3 grains. The preparation "trypsogen," referred to in the text, is put up in 5-grain tablets.

Testicles.—Orchitic extract is given in doses ranging from 2 to 4 grains, according to the individual preparation. There are also many liquid preparations on the market, likewise products combining this extract with that of the central nervous system. (See Pluriglandular Extracts.)

Ovary.—Extracts of the corpus luteum are usually administered. The average dose is 3 grains.

Mammæ.—The mammary gland preparations have been mainly used for menorrhagia, as an antagonist to the ovarian secretion (see note on pluriglandular preparations), and in the treatment of uterine fibroids. The dose for the first of these purposes should begin at 5 grains and be increased to about 10 grains; to antagonize hypo-oöphorism, the dose must necessarily be elastic; while for the treatment of uterine fibroids the dose is about the same as that for menorrhagia, but varies according to different authorities.

Prostate.—The preparations of the prostate gland are given in doses ranging from $\frac{1}{2}$ to 3 grains.

Thymus.—The dose varies from 3 to 10 grains. It is stated that care should be exercised in prescribing this extract to gouty patients, on account of its richness in nucleins.

Intestine.—Preparations of the duodenum containing pro-secretin are given in doses of 1 to 3 grains. "Secretogen" tablets contain duodenal pro-secretin and succus entericus.

Liver.—The dose varies enormously with different preparations. Large doses may be given, however, even up to 1 drachm, of the vacuum-dried extract. An average dose, however, is 15 grains three or four times a day.

The dose of bile is from 3 to 5 grains; 10 grains is a purgative dose.

Spleen.—Of the solid extract, 5 grains is an average dose; up to 15 minims of the liquid preparations.

Parathyroid.—In exophthalmic goitre, paralysis agitans, chorea, and epilepsy, the dose is from $\frac{1}{50}$ to $\frac{1}{30}$ grain.

Pluriglandular Preparations.—These, of course, present many different combinations. Perhaps the most usual combination is that of the extracts of nervous tissue—the brain and spinal cord—with extracts of the gonads. To such a preparation some manufacturers add extracts of the thyroid, pituitary, or thymus. In the author's opinion, this is to be deprecated, as the reaction of the patient is difficult to judge in the presence of such complicating compounds. The correlation of extracts of the ovary and breasts is likewise unwise, as their actions are by no means similar; in fact, in some cases—*e.g.*, the use of mammary extract in menorrhagia—their effects are opposed. On the other hand, there is much to be said in favour of pluriglandular therapy, as many "neurasthenic" conditions are undoubtedly examples of hypo-endocrinism, and as such benefit from this form of therapy.

Care is needed, however, in commencing "tonic" treatment by these means, as a condition of irritability—the reaction from the torpor of hypo-endocrinism—is apt to result in a certain proportion of cases when these preparations are first administered. Nevertheless, the help they can give is very great, especially in functional neuroses; but the preparation must be chosen with care, and the reaction of the patient to this form of medication noted, so that any changes may not escape notice, as it may be necessary to alter the component parts of the product, and rearrange, so to speak, the proportions of its constituents.

The present writer is in the habit of picking out the extracts which he considers are required in an individual case, and combining them in the proportions which seem most suitable. In this way a more accurate dosage is possible, and the constituents may be readjusted should this be necessary.

This, then, is a brief summary of the more important organic extracts which are available for administration, although the list is by no means exhaustive. Every medical man encounters from time to time cases which are not relieved or even benefited by ordinary methods of treatment. In many of these patients relief would be afforded, if not actual cure, by organo-therapy.

In the following chapter some practical points in hormone-therapy are dealt with. It is hoped that this chapter will be of help to those unfamiliar with the practice of organo-therapy.

Reference.

[1] Harrower, Practical Hormone-Therapy, pp. 22, 23.

CHAPTER XIV

PRACTICAL POINTS IN HORMONE-THERAPY

THERE are many disorders where endocrine disturbance may be expected, but where the signs indicative of gross disorganization are lacking.

In some instances there are symptoms suggestive of a state of hypothyroidism, but there are also present features which contradict such a diagnosis, and even contra-indicate the administration of thyroid extract. Those cases in which help can be derived from the history are, of course, easier so far as the commencement of treatment by organo-therapy is concerned.

So far as the practical experience of the present writer is concerned, the utilization of organic extracts requires nice judgment if we are to obtain satisfactory results. The data are often so few or so slight in character, and our exact knowledge of the small signs of pluriglandular disturbance is so deficient, that at this stage in the progress of this method of treatment the physician must rely upon his practical handling of the individual case, to compensate for the lack of exactness in diagnosis. Nevertheless, if we judiciously weigh the evidence in any given case, and if we are possessed of such knowledge as experimental physiology and clinical practice can give us, we shall very often find that we can help patients who are not making progress under other methods of treatment. We should learn to judge how long a particular extract should be persevered with; what signs of its action to look for; and when we should alter its dose or change the prescription. In this relation, organo-therapy is analogous to the utilization of the inorganic drugs in the pharmacopœia; it is necessary to know, not only the physiological effects of our minerals, but also any toxicological results which might accrue were the dose unsuitable.

The diagnosis of disorders, in which the secretion of one gland is patently deficient, is relatively a simple matter, although treatment does not necessarily end when one has ordered an extract of the gland in a suitable dose. Better results may often be obtained by giving a pluriglandular preparation, for in some cases the outstanding deficiency has led to secondary complications. Such a syndrome is better dealt with by a combination of extracts. But the larger proportion of patients present no such helpful guide as a single glaring defect. If this were the case we should be able to diagnose our patients in the streets, as, for example, it is possible to do with acromegalics and subthyroidics. There are, speaking in general terms, two systems which will bear a close scrutiny whenever we prescribe an organic extract; and these systems are intimately related to each other. They are the cardiovascular, and the excretory; and from the study of how these two units are behaving much information can be obtained. It is not necessary to point out, and still more unnecessary to apologize for, the fact that many of the statements in this chapter are elaborated upon what may be regarded as slender foundations. In a science as youthful as this, we must utilize what lies to our hands, discarding what is worthless as something better is found.

In approaching a particular case we have first to decide whether there is an endocrine disturbance; next, which part of the hormone-balance is upset; then, whether it is a disturbance in which organotherapy would be useful; and, finally, which product or combination of products would be suitable.

To take an example in order to make our meaning clear. Juvenile obesity is a condition by no means rare. With it are associated, in a certain proportion of cases, physical mal-development and mental backwardness. There are frequently no very tangible physical signs apart from the general clinical picture. Now take two children, both belonging to this group; one will do well on thyroid, the other will make no progress, however carefully and skilfully the extract is handled. The extract here may have been given, either because a diagnosis of hypothyroidism has been arrived at, or because of its physiological effects.

To continue with our example. What treatment is to be adopted in the case of the second child? We know that hypopituitarism presents features similar to those of hypothyroidism. Pituitary extract may serve to regulate the disordered metabolism. If so, the child will improve mentally as well as physically; but sometimes in these cases—and most practitioners can recall cases of this kind—both thyroid and pituitary fail. Here we arrive at the utility of an extract from its third aspect—namely, empiricism. Physiology teaches us that the thymus and the gonads are, so far as growth is concerned, antagonistic, and that the former wanes as the latter waxes. If the child is small of stature, extract of thymus might help, inasmuch as it improves the general nutrition and stimulates growth. Or, again, if the symptoms are associated with delayed puberty, extract of the ovary or corpus luteum might help in the regulation of metabolism and the promotion of adequate oxidation of the tissues. Again, we might summon help from the chromaffin tissue, assume that some passing infection has produced a hypo-adrenia, and prescribe adrenal extract. Finally, we might order a compound—the pluriglandular product.

I have purposely put the case in this way and its treatment, because it is a good example of the problems which face the organo-therapist and the possibilities of treatment between which he has to decide.

He will remember that in many cases of submyxœdema the anterior lobe of the pituitary has been found to be enlarged; and we have already pointed out that this may be an attempt to prevent the stagnation consequent upon deficiency of thyroid. If, however, pituitary extract fails to help the condition, we must assume that another hormone is required and must endeavour to supply it. It is wise to bear in mind that there is a definite complementary action among the internal secretions, and that deficiency of one hormone can be compensated for by the vicarious overtime of another.

There is no need to labour this point. It will be obvious that many of the indications upon which we prescribe organic extracts are of the flimsiest structure. This must needs be so in any new method, and time and experience alone will enable us to "hit the bull's-eye" the first time; indeed, we are sometimes fortunate if we hit the target at all, when we consider the disadvantages under which we labour.

The Utility of Empirical Prescribing.

There are certain extracts to be found in the catalogues of most manufacturers, the utility of which is not supported by physiological evidence, at any rate not conclusively so. Of these, splenic extract is an example. It is recommended for use in anæmia and chlorosis, and for raising the resistance to infection, notably in tuberculosis. It is stated that it stimulates nutrition and augments the body-weight, increasing at the same time the leucocyte count. How does the evidence of physiologists support this? Recent experiments on the internal secretions, reported in Sajous's work, show that the spleen is concerned in digestion; the experiments which are particularly convincing in this connection are those of Schiff and

Herzen. These observers showed that pancreatic digestion was impaired or stopped when the splenic vessels had been ligatured. Sajous says: "It is evident that, if—as believed by Schiff and Herzen—the circulatory cycle must be traversed by the splenic ferment before the pancreas can be influenced by it, this ferment will merely pass through the pancreas without in any way converting trypsinogen into trypsin, and fruitlessly re-enter the splenic venous current."* This author continues to develop the theory that the spleen is concerned in the processes of digestion, in which function it stands intimately related to the pancreas. Without further describing the evidence—which is long and technical—we may say that such evidence as has been produced by recent laboratory work is on the side of the argument that the spleen possesses an internal secretion which is concerned in digestion.

Now for the practical question. To what utility can extracts of the spleen be put? On p. 227 we refer to the hormone which has a stimulating effect upon peristalsis. This substance is stored in the spleen, and is in use for the treatment of chronic constipation. After injection into an animal the increase in peristalsis can be seen to be very marked. In one patient whom the present writer had under his care hypodermic injections of splenic extract were ordered to endeavour to raise his resistance, as there was an infection, the nature of which was not diagnosed,

* P. 393.

which was progressive and causing anæmia, loss of weight, and general bodily weakness. The effect of this treatment was steadily to raise the body-weight and strength, and to abolish the nocturnal temperature and sweats. But perhaps the most interesting result achieved was that the constipation and indigestion, which was of long standing, improved markedly as the treatment went on, and after some months the patient required practically no aperients, had lost his "yellow" colour (the latter a sure sign of toxæmia), and no longer suffered from indigestion.

This case was an example of the utilization of an extract, without very much physiological support. For, although the spleen is known to be concerned in the replacement of the white cells and the destruction of used-up cells, the evidence that its extracts are therapeutically valuable is of the slightest. From the histological standpoint it cannot be called a ductless gland because it is not composed of epithelial cells; nevertheless, as we have already said, evidence is being collected to show that it is concerned in the formation of internal secretory substances.

Administration of splenic extract has been attended with success in several disorders. In the case quoted above, the main factor, in the present writer's opinion, was the presence of a toxæmia, and this was in all probability of an intestinal origin. It is suggested, therefore, that the injections of splenic extract helped to neutralize these, and to raise the hæmic resistances, This is, of course, speculation; but if such treatment after a more extended trial, can be shown to be efficacious, we may perhaps be able to add to our therapeutic weapons in the treatment of alimentary toxæmia.

The use of splenic extract in the treatment of tuberculosis is well known. Boyle, of Cannes, speaks in the highest terms of the success which has attended its employment in the treatment of this disorder, and his results certainly bear out his contentions. Other observers have reported success following upon this method of treatment.

Extracts of spleen have been utilized in diseases of the spleen, and in patients where the spleen is enlarged. It has also been employed in cases of typhoid, malaria, and in blood diseases. In the latter its influence is mainly upon the leucocyte count; and that this result is not obtained by the nuclein content of the extract is shown by the fact that other extracts—namely, thyroid, liver, and kidney—had no such effect.* In many cases of toxæmia, extract of spleen will be helpful, and this is, perhaps, particularly true in intestinal toxæmia. In the patient referred to above, injections of splenic extract (British Organo-therapy Co.) were employed and were divided into several courses of a dozen, three being given a week, with an interval of a fortnight at the end of each course. No undue reaction—either local or general—was noticed at any time; but on one occasion when the injections were omitted for rather longer than usual (during the

* Quoted in "Practical Hormone-Therapy," by H. Harrower, p. 132.

earlier part of the treatment), the patient began to lose weight.

We have already referred to the utility of adrenal extract. It may be helpful here to indicate in a little more detail practical points in its administration.

The present writer is in the habit of commencing with small doses of the extract by mouth (*e.g.*, 2-gr. capsule, British Organo-therapy Co., or ½ drachm of the Elixir, Allen and Hanbury), and gradually increasing this dose until the maximum recommended by the manufacturer of the particular preparation is reached. If no undue reaction is recorded, and if the patient has shown no signs of improvement, injections can be given twice or thrice a week in the buttock. In the "exhaustion" cases already mentioned, signs of hypo-adrenia are often found, and in some instances the presence of indicanuria points to the concurrent existence of intestinal mal-assimilation or stasis. It may be that this latter condition is the cause of the adrenal exhaustion, but, in any case, such patients frequently derive much help from adrenal therapy.

In some instances (and this has been recommended by other writers on this subject) the combination of adrenal and pituitary extracts is more successful than either singly. It is often a good plan to administer pituitary extract (whole gland) by the mouth twice or thrice daily, and adrenal extract intramuscularly twice or thrice a week. In obese patients (it has been said that the obese neurasthenic is the most troublesome to treat) extract of the anterior lobe of the pituitary gland is preferable, as its effect upon metabolism is more speedily noticed. Small doses of thyroid gland —$\frac{1}{4}$ to $\frac{1}{2}$ grain at bed-time—assist excretion without interfering with the routine treatment.

It may be mentioned here that the contra-indications to the administration of adrenal gland must be borne in mind in every case before even oral doses are given. Arterio-sclerosis, or persistent hyperpiesis,* diabetes, or glycosuria, phthisis, hæmoptysis, and many cases where digestive disturbances are in evidence, are unsuitable for adrenal therapy. It is also somewhat risky to prescribe this extract where the nervous system is unstable, where the patient is emotional and excitable, although adrenal therapy is often recommended to overcome the physical state ensuing after psychical strain.

Backward children can often be helped by organotherapy. In Chapter VI. we refer to two cases of this kind reported by Magnier, which had benefited markedly by the administration of anterior lobe of the pituitary. If this fails, or if it appears to be contra-indicated, other extracts are available. Let me draw attention to a type of child frequently encountered in the consulting-room. The mother brings the child complaining that he or she is dull, "cannot understand like other children," is not making progress at school, and, perhaps, will not play or mix with other children

* We have pointed out that several sphygmanometric readings are necessary in these cases, as the blood-pressure varies markedly from time to time.

of his own age. On examination, the child has what Magnier calls a "sheepish look," is obviously of sluggish mentality, answers questions slowly and is generally stolid, mentally and physically. There is sometimes a history of bed-wetting, or it is even a symptom up to date. The limbs are often clumsy, and I have frequently been struck by the large size of the bones, more particularly those forming the knee-joint. The skin of such children is smooth and singularly hairless, and the child or mother will admit on questioning that he does not sweat like ordinary children.

This type of case I regard as being due to hypopituitarism, for two reasons. First, because the symptoms point in that direction, although these obviously vary according to the stage at which one sees the patient; second, because of the improvement which follows the exhibition of pituitary extract. It may be that the patient is suffering from dyspituitarism;* and that symptoms of past hyperpituitarism are mingled with present hypopituitarism. This, it seems to me, accounts for the heterogeneous and contradictory features of many of these cases, seen from the point of view of the organo-therapist; and it makes the choice of an initial treatment a difficult matter.

There is, however, one feature of these patients which is definite, and which indicates plainly a line of treat-

* See p. 138 for a reference to this condition. Also compare the cases just described with Frohlich's syndrome, or dystrophia adiposo-genitalis.

ment, and that is inertia shown mentally by the slowness of comprehension, and physically by the sluggishness of the circulation, the deficient elimination, and the retention of metabolic products in the form of fat.

Thyroid, pituitary, and extracts of the gonads all improve this condition, and the decision as to which shall be utilized in an individual case depends upon the correlation of other symptoms. The calcium metabolism of the body is profoundly disturbed in these patients; in fact, they present the opposite picture clinically to the bright-eyed, eager, and restless hyperthyroidic. Bradley Figgis describes the backward child we are discussing: "At school, the dull, slow-witted, apathetic boy, with heavy bones and a tendency to grossness of body, as well as his eager, restless, impulsive brother, with no great power of concentration or perseverance, are both amenable to the action of these secretions affecting calcium and general metabolism. It may yet be possible to add a cubit to one's stature by a course of pituitarin or other extract. At puberty, and during sexual life, abnormalities of growth and functioning and morbid tendencies may be corrected by pituitary, thyroid, mammary, or ovarian extracts."*

So large a part does the pituitary play during development that one is almost inclined to commence the organo-therapeutic treatment of these cases with extract of this gland, assisted by small doses of thyroid

* "The Empire of the Ductless Glands," *The Medical Press*, September 20, 1920, p. 249.

extract. But the thymus has given good results in some cases; while pluriglandular preparations can justly claim our attention if only on account of the wider field they occupy.

I have treated cases of this nature with pitglandin, a preparation of the anterior lobe of the pituitary, with good results. I have also employed the same preparation in obesity in adults.

A condition analogous to this, but occurring in adolescence, and often difficult to ameliorate by ordinary measures, can frequently be improved by organo-therapy. In one patient under my care, a boy of sixteen, there is absence of one testicle (removed during an operation), while the other has been stitched inside the peritoneal cavity. This patient has been taking a pluriglandular preparation for a very long time, as, if he omits this treatment, he begins to develope a sluggish mentality, to be unable to do his school work, and to suffer from obesity, chilblains, etc.

The fact that better results are obtained by a mixed preparation than by orchitic extract alone suggests that the absence of the secretion of the interstitial gland has upset other of the internal secretions.

The case reported in the last chapter, where the boy of seven years, suffering from double undescended testis, was treated by thymus gland and hormotone in combination, with the result that the testes had descended after five weeks, suggests that extracts other than those of the gonads are worthy of employment in these cases.

Perhaps no field exists offering such a wide opening to the organo-therapist as that of the backward child; and any physician who has treated patients by these methods will agree that during development full use can and should be made of the help to be derived from organo-therapy.

During adolescence and the third and fourth decades of life, cases are encountered in many ways analogous to the backward child just described. These are frequently instances of hypothyroidism, but they are mentioned here in order that points in their treatment may be referred to. The patient—often a woman—complains of physical and mental languor, associated with increase in the body-weight; or some "rheumatic" affection such as stiff joints, lumbago, or "muscular rheumatism," is a common concurrence. The elimination in these patients is often faulty; they complain of constipation and digestive disturbances, the urine is concentrated and contains phosphates, urates, and sometimes indican; while they will probably admit that they rarely, if ever, sweat. It is generally a matter of difficulty to establish a definite onset, and perhaps even careful questioning will not succeed in eliciting a definite period during which the health has been bad. On the other hand, there may be details in the history worthy of note from the etiological point of view. Thus, a patient presenting the above features recently informed the present writer that all these symptoms were at the worst during the catamenia, in fact were comparatively negligible except at such times.

Such a syndrome might be explained on the ground of reflex disturbance of function, the blame being placed upon the nervous system. From the therapeutic view-point something more helpful is required, and this can be supplied by organo-therapy. In all such cases as these the basis of treatment should be founded upon the aim of increasing elimination. Exactly how this can be accomplished will depend upon the results of the physical examination. Assuming that such means as laxatives, diet, and adequate exercise have been instituted to increase elimination, we must consider which of the "big three" among the endocrine eliminants should be prescribed. Thyroid, pituitary, or the gonads—one or more of these will be required. If there are any indications of hypothyroidism upon examination, treatment should commence by small doses of thyroid extract given at bedtime. Pituitary extract, whole gland or anterior lobe, is of real value in these patients, and can be given in conjunction with the thyroid. While it is not possible to lay down any hard-and-fast rule as to dosage, ½ grain of thyroid at bedtime, and from 1½ to 2½ grains of pituitary extract twice daily is somewhere around what will be found to be suitable in the average case.

There are several ways in which thyroid extract can be helpfully administered to patients who require it over a long period. One method which has gained popularity is to give the extract for three weeks every month, and omit it for one week. This is designed to prevent undue accumulation of the iodothyrin, which has sometimes been found to lead to symptoms such as tremors and jumpiness. Another method is to forbid the patient to take the extract at any other time except the last thing at night, by which means rest in the recumbent position is assured after the dose, and larger doses can be given without risk of palpitation or other unpleasant sequelæ. This I have found to be a good plan, and I also insist upon the dose being reduced or omitted altogether in the event of the patient being called upon to undergo undue exertion of either mind or body.

The lymphatic type of patient whom we have described improves markedly under thyroid treatment; the weight decreases, the functions improve, and the feeling of well-being is again experienced. A note of warning is perhaps needed as to the administration of too generous doses; not only is it dangerous, but it frequently defeats its own object, for such patients improve much more steadily, if we are content to take our time over the treatment, than if we are impatient to see results. Again, if symptoms of "nervousness" develope, it is better to leave off the thyroid for a week or two and insist upon increased rest until the condition improves; it is not uncommon for such symptoms to manifest themselves while thyroid-therapy is in progress.

The rule in all organo-therapy should be a small initial dose, a gradual increase, and a cessation if symptoms develope while the treatment is in progress.

CHAPTER XV

CONCLUSIONS

Having dealt with the pathology and treatment of the organs of internal secretion, and having briefly outlined the organic extracts which may be utilized in the treatment of disease, it may not be out of place at this point to discuss the present place of hormone-therapy in medicine.

Not many years ago an eminent physician, in speaking of the use of medicines, said that in prescribing a drug a medical man was putting a substance of whose properties he knew little into a body about which he knew less. This may be only too true with reference to the administration of inorganic chemicals, or, rather, with reference to certain inorganic chemicals; but now that organo-therapy has become an established method of treatment, it can scarcely be applied indiscriminately to all forms of prescribing. But it cannot be denied that much drug-therapy is empirical, and is resorted to in the hope of counteracting morbid conditions of the body, and that much of such treatment would be quite useless were it not accompanied by the hope and faith of the patient.

In prescribing organic extracts, however, we are endeavouring to counteract morbid states by administering the substance the deficiency of which we believe to have caused the condition. We gather together the salient features of an individual case, and compare the syndrome with that which is known to be present in derangements definitely due to disturbances of the hormone balance. If this points decidedly to a deficiency of one hormone the path is clear, and the result will be steady improvement to cure. But if a multiple disturbance is present, and it must be remembered that this is very often the case, the course of the treatment will not be so smooth, neither can the first combination be expected to prove successful.

Nevertheless, even with this class of case, the adoption of organo-therapy is less speculative than is the prescription of many inorganic remedies, which, in ameliorating one symptom, are prone to initiate another. With obvious hypothyroidism or hypopituitarism, the only remedy which will give a speedy and satisfactory cure is the administration of the organic extract whose deficiency has produced the symptoms. But, apart from such straightforward cases as these, there are a host of physical and mental deviations from normal health which may be rectified by this method of treatment.

We have already outlined these, but we desire to emphasize in this chapter that the use of organic preparations is now an established method of treating disease, and one which will undoubtedly form a large part of treatment in the future.

In an article dealing with the question of the treatment of disease which was published recently in a prominent journal, the opinion was expressed that the majority of chronic diseases of middle age could only be palliated—that their cure was impossible. The writer proceeded to emphasize the fact that these diseases arise during early youth, and that our ignorance of the origin of chronic disease is profound. This latter statement is, unfortunately, correct; but the first clause which we have quoted was probably truer twenty years ago than it is now. For every year that passes increases our knowledge of the efficacy of modern methods of treatment, and not least among these we must class organo-therapy. Before the discovery that myxœdema owed its origin to atrophy of the thyroid gland, and that the symptoms caused thereby yielded to the administration of extracts of this gland, the features of this malady were hopelessly intangible, and their treatment, either as individual symptoms or a syndrome, impossible. This disease may be included among those which the writer of this article had in mind; but although the actual cause of the atrophy is unknown, it is quite untrue to say that its palliation only is possible. For both in the grosser disease myxœdema and in the lesser malady submyxœdema, the administration of thyroid gland is curative—in so far as the disappearance of symptoms constitutes a cure. It is quite true that the treatment must be continued, even throughout life, but so long as it prevents the disease from persevering, we have achieved what may be called a cure.

This is only one disease, and one among thousands; but it is nowadays curable, and it is probable that, with the advance of our knowledge on these lines, many other lesions included in the past among the incurable or chronic disorders will yield to modern therapy. Not only the vague neuroses—the neurasthenic, the neurotic, or the hypersensitive patients, whose existence is due to the civilization we boast of—but diseases which, in the past, have left their victims more or less crippled for life, will in the future probably be treated so that they no longer maim permanently.

Many of these diseases are accountable for the derangements seen in middle age, and by the time advice is sought the machine can only be repaired, not restored. But the repairs will be less needed when our knowledge of the treatment of the diseases incidental to childhood is improved, and it may be that the endocrine glands will figure largely in such improvement. If, for example, we can increase the defences of the body against infection by the administration of an organic extract (as is now done in the case of tuberculosis), we shall have developed a weapon against which the onslaught of micro-organisms will be weakened, if not defeated. In which case the germs responsible for the exanthemata, with their damaging sequelæ, will find their task less easy than formerly.

Even the organic changes which we are accustomed to regard as inseparable from middle and old age may be remedied or averted by the employment of organic extracts. An example will serve to make our meaning clearer. The complex metabolism of the body appears to be regulated by the organs of internal secretion; a deficiency or excess of one of these important correlators is able so to upset the metabolism that substances, often of a noxious nature, are stored in the body instead of being eliminated by the usual channels. In course of time this gradual retention may produce a metabolic disease such as gout or diabetes, and it may assist in the well-known accompanying changes such as are present in chronic interstitial nephritis, in hepatic cirrhosis, in fibrositis, and numberless other deviations from normal health. If deficient elimination is treated in the future from the commencement —*i.e.*, when the first signs of metabolic disturbance are present—by the exhibition of one of the organic extracts which regulate metabolism, instead of by occasional purgation, we may well hope that the "diseases of middle age, which arise during infancy or adolescence," may no longer be regarded as a necessary concomitant of advancing years.

This, then, is what we mean by the statement that our knowledge of organo-therapy may conceivably be extended to the avoidance of organic lesions in the near future. We have already pointed out that the thyroid, pituitary, and pancreas, to mention three out of many, are intimately concerned in the control of metabolism, and that a deficiency in secretion of either of the first two glands results in a storage of waste products, in thickenings of the subcutaneous tissues, and in the retention of chemical substances which should leave the body. Such conditions disappear upon the administration of the extracts of these organs.

By comparing these syndromes with that which accompanies, let us say, "idiopathic" obesity, or the gouty diathesis, we must at once be struck by the similarity of the two pictures. Therefore it does not seem to be stretching a point to say that, were these latter diseases suitably treated in the early stages, it would be possible so to regulate metabolism and to effect adequate elimination that the system would be restored to the *status quo ante*. The advanced stages of faulty elimination which are now encountered in the out-patient and consulting-room could thereby be avoided.

This is, doubtless, looking far ahead; but if we are justified in assuming that the majority of the diseases of middle age date from childhood, and are in consequence incurable, it behoves us to look around for a means of avoiding such a lamentable state of affairs.

Slight degrees of hypo-endocrinism usually recover without aid from opo-therapy. If, however, they do not, it is conceivable that the perversion of metabolism commences from such a condition, initiated, let us say, by an infectious disease. The faulty elimination is at first slight, but increases; the individual takes less exercise as his age advances, and when he reaches his fourth decade, he is probably prematurely old, physically unfit, with yet no definite signs of organic disease. Nevertheless, another ten years may have altered his condition for the worse: the blood-pressure may be high, the urine show a trace of albumin and a decidedly acid reaction, the joints be stiff, the hirsutes scanty, and the skin dry and its appendages lifeless.

Every practitioner is familiar with such a type—a man aged at fifty! Even now he will feel benefit in many cases by an organic remedy. But twenty years before what a difference the adjustment of his hormone balance would have made to his future health and comfort!

The present writer has seen many ailments, slight in themselves, but of some considerable tenacity, disappear upon the administration of thyroid extract. He has also seen patients, who admit that "there is nothing wrong with them," attain a degree of health which they had not known for years from the same treatment. He is convinced, therefore, that a great future lies in front of organo-therapy; but it must be given every chance: to wait until the patient's system has become altered by years of faulty elimination is to deny the rational remedy a fair chance of success.

This, then, is a plea for the early use of organic extracts in every case where their administration appears to be indicated. By their prompt use there can be small doubt that many derangements will be righted before they can become diseases, and it will not be necessary for our successors in medical practice to make the lamentable confession recorded by the writer of the article referred to above.

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This book has aimed at presenting to the reader a short survey of the organs of internal secretion, their diseases, and the uses to which preparations of the hormone-producing glands, and of organic tissue generally, may be put. At the close of this chapter will be found a short bibliography, and the reader anxious for a fuller account of this subject is referred to the works there mentioned. Many of these deal with one gland only, while some are general surveys of organo-therapy.

Among the large treatises which have been published in the last few years is Cushing's book on the pituitary gland; Léopold-Levi and H. de Rothschild's study of thyroid deficiency; and a monumental work by Allen on glycosuria and diabetes. In "Internal Secretions and the Principles of Medicine," Sajous has supplied a work which includes the study of the internal secretions and the disorders which arise as a result of a faulty endocrine working. This author lays especial stress upon the importance of the suprarenal secretion, and the part it plays in the bodily harmony.

The study of lengthy and exhaustive treatises such as these is often impossible for the busy practitioner, and the present volume has attempted to summarize the subject in as brief a space as is possible.

For those desirous of obtaining the latest information which is available on the practical side of the subject, Harrower's book well repays a careful perusal. Not only has this author collected a large amount of literature dealing with the internal secretions, but he has produced a book which is of really practical help to those desirous of prescribing organic extracts.

For a histological survey, Schäfer's work entitled "The Endocrine Glands" should be consulted; while Biedl's book on the "Internal Secretory Organs" is a careful and thorough account of the subject from all standpoints, although it does not deal with hormone-therapy.

A list of notable contributions to this subject is appended.

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