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PRACTICAL HORMONE THERAPY

H. R. Harrower

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PRACTICAL HORMONE THERAPY

A MANUAL OF ORGANOTHERAPY FOR GENERAL PRACTITIONERS

BY

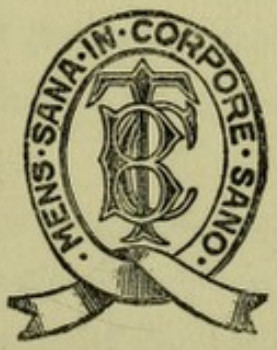
HENRY R. HARROWER, M.D.

SOMETIME PROFESSOR OF CLINICAL DIAGNOSIS, LOYOLA UNIVERSITY, CHICAGO;
FELLOW OF THE ROYAL SOCIETY OF MEDICINE; FELLOW OF
THE AMERICAN MEDICAL ASSOCIATION

WITH FOREWORD BY

PROFESSOR DR. ARTUR BIEDL

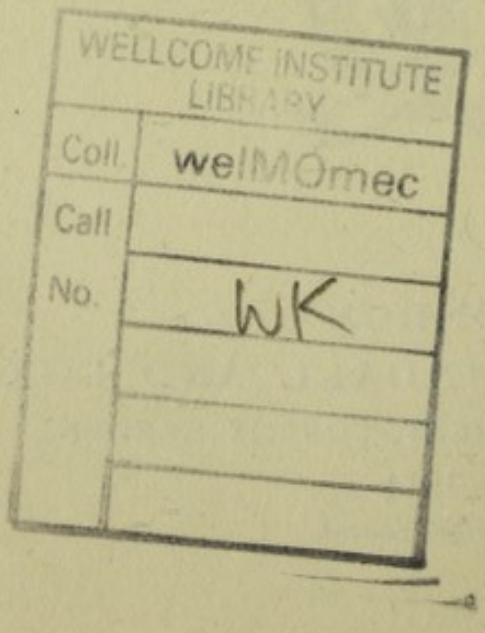
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FOREWORD

My dear Colleague,—

I feel greatly honoured in being asked to write a few words of introduction to your book, "Practical Hormone Therapy."

On looking through the proof sheets, I was at once struck with the excellent manner in which you had succeeded in laying before your readers this new branch of therapeutics in a concise and easily understood form.

Hormone Therapy, although its beginnings can be traced back to ancient times, is actually a most recent acquisition, a practical deduction from that new sphere of biological inquiry which is concerned with the Theory of Internal Secretions.

Since I have myself worked on this subject, and have endeavoured to give a clear and concise account of its present state in my own book, you will readily understand that I am perhaps somewhat prejudiced in its favour when I emphasize the importance of internal secretions for the purpose of obtaining a correct insight into the normal and pathological processes. Medical practitioners will have to decide finally whether the deductions drawn from our theoretical observations can be turned to

good account in the diagnosis of diverse complicated pathological conditions, and whether they can be reduced to rational therapeutic methods.

You have now placed in their hands a guide which will enable them to collaborate with us in working out this problem. All those concerned, whether theorists or medical practitioners, will be grateful to you for your labours.

Allow me, my dear colleague, to congratulate you on your work, and to sign myself,

Yours very truly,

PROFESSOR DR. ARTUR BIEDL.

PRAGUE,
May, 1914.

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INTRODUCTION

THE introduction into therapeutics of preparations containing the active principles of the internal secretions is one of the greatest achievements of modern medicine; and the increasing applicability of the hormones as useful factors in the general practice of medicine suggests the collation of much practical information which will epitomize the position of this rapidly advancing branch of therapeutics.

The Title.—With regard to the title of this book, I feel that some explanation is necessary. It is fully admitted that the activity of animal extracts is not due entirely to their hormone content; but at the same time most of this activity is undoubtedly brought about by such bodies, and the title "Hormone Therapy" is concise and convenient. It is gradually being recognized in medical literature as a ready form of expression for the more cumbrous one of "therapeutics of the ductless glands and internal secretions." At the same time I do not propose to limit the scope of the book strictly to its title, for it is proposed to consider several closely allied subjects (bile, the lipoids, etc.).

In the blood there are countless substances of the nature of hormones, related to one another and performing innumerable functions. We have but to think of such phenomena as the production of digestive fluids, the regulation of the nervous system, the change from puberty to

manhood or womanhood, the menopause, the gradual onset of senility, and many other well-known phenomena, to understand why the blood should carry within it countless "chemical messengers," each with a specific object. The fundamental principle of hormone therapeutics, and certainly a most reasonable one, is to supply to the body a certain hormone or combination of hormones which through disease has been diminished or lost.

Some of the statements regarding the therapeutic application of endocrinous preparations are strange, to say the least, for whoever would imagine the use of placental extract as a remedy for alopecia, or of adrenal extract as a cure for seasickness. The story of these and many other remarkable things is to be found in the following pages, and whether these ideas are in everyday use or not does not alter the fact that the hormones are perfectly wonderful therapeutic agents, exceeding in range and activity any drugs at present known.

Medical Scepticism.—As has been the case with practically every new discovery of import, there is still a tendency to look askance upon the use of animal extracts in therapeutics. A few are becoming generally used, but as yet only a few. We all remember the storm of hilarious incredulity with which the first announcement of Roentgen's discovery was received less than twenty years ago. The idea that a living man's skeleton could be photographed seemed too absurd to be considered.

The position of the medical profession is well outlined in the following sentence, requoted from the preface to Sajous's work on the "Internal Secretions": "If any daring member has introduced a subject bearing on medical treatment, it has been with an apologetic air and humble mien, well knowing that if his remarks had any reference to the utility of drugs in the treatment of disease

they would be subjected to good-humoured banter, and received by those sitting in the seat of the scornful with amused incredulity."

The only valid test in the case of hormones, of course, is clinical experience, which may be carried out under conditions which can be repeated by others with comparatively similar results. It is not difficult to find cases suitable for this purpose, nor, for that matter, trustworthy preparations with which to make the tests. We must separate ourselves from those who are satisfied only with extraordinary results from any new remedy or method of treatment, and be content with frequent encouragements and occasional failures.

There is still a widespread tendency on the part of some medical men, at least among those in general practice, to consider that the functions of various organs are controlled principally by the nervous system, and when disorganization of these functions is found, to treat it with remedies and methods calculated to influence them through nervous channels.* Our ideas need broadening, and the study of the hormones and their diverse activities will effect this very quickly.

No subject will prove more enthralling to the interested reader than the possibilities of hormone therapy, not only in the obvious disorders of the endocrinous glands, but in many other diseases evidently amenable to treatment with their products. Nor will the interest wane when plausible theories have become tangible results; for the possibilities of this method are almost limitless and its study not confined to laboratory experiments, nor is its chemical basis dependent on the unsupported experiences of a few enthusiastic investigators.

* This is illustrated by our everyday use of strychnia in conditions requiring stimulation, and morphia where an opposite effect is desired.

Personally, I believe that "opothérapie," as the French have named it—that is to say, the use of organic preparations, the activity of which is dependent upon their contained hormones—is deserving of considerably greater study and application than it has hitherto received, and it seems that in this phase of medicine, at least, British and American physicians are behind their European confrères.

The Present Limited Application of Hormone Therapy.—At present the application of hormone therapy in general practice is the exception rather than the rule, and the exhibition of endocrinous preparations as remedies is, in this country at least, practically confined to the use of preparations from the thyroid, pituitary, and adrenal glands.

It is admitted that much has been accomplished in the past ten years to establish the therapeutic usefulness of certain secretions of the digestive glands, the reproductive glands, and the spleen; but the proportion of general practitioners who avail themselves of remedies of this character is very small, possibly not five per cent.

As a part of my investigation of this subject, I have looked into the frequency, or, rather, the infrequency, of the use of preparations of this character, and if the data obtained from the limited hundreds from whom information has been secured may serve as a criterion, the percentage mentioned above is none too small. On the other hand, in the Continental countries, especially in France, Italy, and Germany (probably in the order mentioned), the whole subject is considered in a much more familiar manner.

There is, then, much truth in the statement that the use of hormones in general practice is *terra incognita* to the majority of medical men, and for this reason a review

of the important advances in certain of these fields may lead to more successful practice through the more thorough control of those conditions which are either directly due to, or at least indirectly associated with, disorganized metabolism.

The Scope of this Book.—The principal object of this book is to broaden the therapeutic horizon and to stimulate the reader to include in his armamentarium such of the hormones as are of proved utility. This work is not a study of the internal secretory organs and their products, but rather an attempt to collate such knowledge as will be useful in *practical therapeutics*. The scope of its contents, therefore, must be limited to a consideration of the remedial value, actual and prospective, of these varied substances. Anatomy, comparative anatomy, physiology (except such as may be essential clearly to set before the reader the philosophy of a certain procedure), pathology (save only where reference to pathologic changes lays emphasis upon a corresponding therapeutic deduction), and biochemistry are left to numerous other books, which already thoroughly cover this part of the subject. Readers who desire further information on this subject are referred to several most excellent and exhaustive works, notably those of Biedl, Beebe, Sajous, and Swale Vincent. Professor Biedl's book—especially the second German edition—is a masterpiece. and is the most complete piece of literature on this subject in any language. To read it through is a postgraduate course in the study of the internal secretory organs. It is true that numerous books are devoted to the internal secretions, and practically every one of them in French, German, Italian, and, of course, English, is in my library. So greatly do I prize these works of reference that it seems advisable to include a list of the more important of them in the appendix, and

opportunity is taken here to recommend them highly and to make due acknowledgment of the assistance they have afforded me in the preparation of this book.

On the other hand, so far as information regarding the *practical application* of the knowledge gained by physiologists in their experimentation with animal extracts is concerned, it is felt that the English literature is lacking. With one or two exceptions, there are no books published on this subject, either in England or the United States, and the exceptions are incomplete and already quite out of date. (An admirable résumé of the subject appeared in the *Prescriber*, a British journal which devoted an entire double number to a review of Hormone Therapy down to the time of issue, April, 1913. I understand that copies of this number are still available.) As a result, one must look to foreign literature or to the literature of manufacturers who specialize in organotherapeutic preparations for information concerning the practical results which have been achieved by such patient experimentation.

The Manufacturer's Position.—A word about the manufacturer may not be amiss. When physiology proves the definite importance of any substance produced by the endocrinous organs, pharmacy immediately attempts to isolate it or at least to prepare it for suitable administration, while therapeutics proceeds to put it to the test and prove or disprove its efficacy in a disease in which it is presumably of service.

Unfortunately there is a tendency on the part of the profession to discount any statements that may be made by those who are avowedly working in this field for their own financial advantage. The other day a prominent professor of medicine in one of the largest English provincial medical colleges assured me that all that the

manufacturers were after was the doctor's money, and he intimated that their interest in science was merely a pretence to cover their mercenary motives. It is undoubtedly true that many ill-considered ideas have been foisted upon the profession, and that many highly coloured and even untrue statements have been made with reference to the ingredients and effectiveness of certain pharmaceutical "specialities"; but in spite of these one cannot deny that medicine is a debtor to the commercialism of those who have deliberately set themselves to discover something new, and thus to add to their prestige in scientific reputation as well as to their prosperity in business. After all, there is a more or less evident mercenary motive beneath all good work, not excepting that of the physician. Ought manufacturers, therefore, to be blamed for considering the bread-and-butter side as well as that which is purely altruistic ?

This is not a record of personal clinical experiences. I cannot even lay claim to great originality in the matter presented. Part of it has been drawn from numerous French works. A majority of the facts have come from technical and medical journals and appear in book form here for the first time. I am aware that in the collection of information from such scattered and polyglot sources, important omissions and even contradictory statements may have crept in. It may easily also have happened that emphasis has been laid on certain points to the exclusion of others of equal importance. My experience with the well-known hormone-bearing preparations is that of an average physician, and my use of such preparations as thymus, kidney, and parathyroid extracts is very limited, while I have never once used extracts of lung, tonsil, prostate, or brain. I am frank to admit that some of the statements which have been incorporated in the

following pages are not yet generally accepted, and some possibly may ultimately prove erroneous; but I am convinced that they have a greater or less degree of warrant of clinical usefulness, and therefore deserve the consideration suggested long since: "Prove all things; hold fast to that which is good."

The Subdivisions of the Book have not been made upon any arbitrary basis. While the recognized anatomical classifications have been followed, the standpoint of convenience has not been ignored. There is still some controversy regarding the actual status of some of the organs of interest to us, and the chromaffin organs are classed in "the nervous system" for want of a better place, while the pituitary gland comes under the same classification, although it is not so long since it was considered a vascular organ. The classification of the spleen with the digestive system may not be in harmony with the ideas of all, especially of those who are wont to consider it as a purely hæmopoietic organ, but the text will explain why this has been done.

The grouping of the thyroids, parathyroids, thymus, kidneys, and tonsils in one class—"the metabolic glands"—may seem incongruous, but it has been adopted for lack of a better way; and because all these organs are certainly closely concerned with the metabolism, even though the principal function of the kidneys may not be of an internal secretory character.

Bibliographic References.—The bibliographies accompanying each chapter are far from complete. It is useless to duplicate, and those who are desirous of studying the subject are reminded that the total of the references in the library books already referred to mounts up into the thousands. In Biedl's English edition the bibliography covers 140 octavo pages; in Swale Vincent's book there

are 2,164 references; while in "Hormone Therapy, 1913" —the special number of the *Prescriber* already referred to—there are 467 references to articles, most of which appeared in 1911-1913, and 177 brief abstracts of recent literature. The bibliographies in this book, therefore, are not extensive, especially those connected with the chapters upon comparatively well-known subjects, such as the thyroid, adrenals, etc. On the other hand, where the reference books seem to me not to have done justice to certain subjects, my bibliographies are more extensive. This is particularly true of the pancreas, spleen, parathyroid, secretin, and pluriglandular extracts. I have dealt with these subjects in original articles published elsewhere.

In verifying several of the references quite a number of additional references were found. The most important of these have been added for the convenience of the interested student.

The Index.—There are numerous works in which the therapeutic indications of various disorders are alphabetically enumerated, and not a few medical men smile when they see, for example, over fifty drugs and combinations specified in Wellcome's "Excerpta Therapeutica" as being useful in tonsillitis. In spite of this tendency to deprecate therapeutic tables—it is admitted that efficacious treatment is dependent on broad, general knowledge and experience, and that a novice cannot expect to be successful simply by selecting a certain table of therapeutic indications and applying them, hit or miss—it has seemed advisable to incorporate with the index a brief and suggestive list in alphabetical order of the commoner diseases with their opotherapeutic indications. An attempt has been made to refer to the particular page in which the general considerations, and so on, are to be

found, thus making an index, as well as a therapeutic index. It must be understood, though, that I have no intention of being arbitrary, and that the main reason for preparing this index has been that it may perhaps stimulate a new train of thought, and the interested investigator may thus be led into certain lines of study, which, without the index, he possibly might have overlooked.

The Author's Acknowledgments.—I have an especially large number of acknowledgments to make. In order that my enthusiasm might not lead me astray I conceived the idea of submitting several of the units which form this book to authorities for criticism. I am under considerable obligations to a number of prominent men, whose names are well known to medical readers.

First and foremost I have to thank Professor Biedl of Vienna for the benefits that have accrued from reading his book, and also for the honour he does me in writing the preface, and in criticizing the three preliminary chapters. To the following gentlemen I am indebted for their having read and criticized the chapters the numbers of which immediately follow each name: Dr. Ch. Bayle of Cannes (IX.); Prof. S. P. Beebe (V.) and Dr. W. N. Berkeley of New York (XIV. and XX.); Prof. Paul Carnot of Paris (XI.); Prof. C. A. Ewald of Berlin (V.); Dr. E. Hertoghe of Antwerp (XIII.); Prof. Howard A. Kelly of Baltimore (XXIV.); Prof. R. Lépine of Lyons (VII.); Prof. G. R. Murray of Manchester (XIII.); Dr. C. E. de M. Sajous of Philadelphia (XVIII.); Sir Edward A. Schäfer of Edinburgh (XIX.); Prof. E. H. Starling (V.) and Dr. Leonard Williams of London (XIII.); and Dr. G. Zuelzer of Berlin (X.).

Finally, to Dr. Kenneth W. Millican I must express my thanks for his helpful revision of the manuscript, and to

Mr. Thomas Stephenson, editor of the *Prescriber* (Edinburgh), for assistance with the proofs and make-up of the book.

In presenting this book to the profession it is with the sincere hope that the information gathered in the pages which follow may serve to lead many to a fuller appreciation of *the therapeutic possibilities of hormones in the routine work of the average medical man.*

H. R. H.

London,
May, 1914.

PRACTICAL HORMONE THERAPY

CHAPTER I

HORMONES: THEIR DISCOVERY, PRODUCTION, AND ACTION

The Antiquity of Animal Therapy—The Origin of Scientific Endocrinology—The Application of this Knowledge in Therapeutics—A Recent Estimate of the Basis of Internal Secretory Therapeutics—Charlatanism and Animal Therapy—The Scientific Establishment of Hormone Action—Starling's Conception of the Hormones—Definitions of the Term "Hormone"—A Classification of Hormones—The Present List of Known Hormones—A Comparison of Hormones and Enzymes—The Selective Action of the Hormones—The Rôle of the Blood-Plasma.

MEDICINE, like every branch of science, is constantly changing. Our knowledge is being increased at such a rate that the advance of a single decade suffices entirely to revolutionize our conceptions. Nowhere has this transition been more apparent than in therapeutics. What would our present-day therapists do if they had to revert to the methods of, say, twenty-five years ago? What should we do without the X ray, the numerous synthetics, the *sterilisans magna* of Ehrlich, the bacterins, or the internal secretions? The rise and development of "hormone therapy" is a great achievement, and the facts of the present are destined to be outshone by the prospects of the future, empirical though they still may

seem to be. "*Hormones are to physiology what radium is to chemistry.*"

The Antiquity of Animal Therapy.—The use of animal organs in the treatment of disease is as old as medicine itself. It is recorded that the ancient Egyptians treated various diseases by means of animal organs or secretions, and in the Ayurvedic writings of Susruta, who lived some time between 400 and 500 B.C., mention is made of the use of orchitic substance in the treatment of impotence. This is probably the earliest specific reference to organotherapy, and from that time it has never been long absent from the literature relating to "medicine" or the healing art. The works of Pliny and Galen show that both those writers had vague notions of the possible presence in certain organs of substances having a regulating action on the functions of similar organs, and contain numerous references to the employment of various animal preparations in the treatment of disease.

From the writings of Hippocrates it is clear that he considered many diseases a result of various "humours," and looked to the corresponding healthy organs of animals for a means of relief. It was natural, then, that organotherapy should be a prominent part of medical practice as it was then.

But the more recent discovery of the wonderful power of control of the body found to reside in the central nervous system quickly overshadowed the crude and absurd notions of the ancients, and from that time the "humoral theory" was quite discarded. Now, however, the pendulum is swinging back, for it has been discovered that the nervous system is not alone in its direction of the functions of the body.

The principle of *similia similibus curantur*, which is the basis of Halmemann's system of homœopathy, has a like-

ness to the principles of organotherapy which have come to us down through the centuries, and, to say the least, it is considerably more pleasant so far as the palate is concerned. The animal therapy of the past is not nice to think of, and the more repulsive forms of animal preparations long held sway. Even at the present day we have such unsavoury animal products as cod-liver oil still enjoying the full benefit of official recognition.

Of course the use of all these remedies is empirical. Indeed, there was a tinge of superstition in many of the cures—that superstition which allows the ignorant to attain by intuition what the learned can arrive at only after years of toil and study.

The Origin of Scientific Endocrinology.—The beginning of the scientific study of the endocrinous organs dates from 1849 or 1850, when Berthold[1] first hinted at the fundamental position of the ductless glands. About five years later the famous Claude Bérnard,[2] whose centenary has just been (1913) celebrated, substantiated this suggestion, and by his well-directed enthusiasm laid the foundation of an entirely new science. This celebrated French scholar is generally conceded to have been the first exponent of the physiologic influence of the internal secretions. As a result of his labours our knowledge of human chemistry, and of the influence of the internal secretions upon it, has become by no means inconsiderable; and, if one can judge by the literature devoted to this subject, it is advancing "at a rate which even the most sanguine advocates of this line of research could not but deem astounding."

The Application of this Knowledge in Therapeutics.—Some twenty or twenty-two years ago a new phase of so-called rational therapeutics sprang up—a system wherein gland substances were administered in cases

where disease was believed to be due to deficient secretion of that particular organ. This doctrine was first put to a practical test by Brown-Séquard,[3] also of Paris, and his experiences with testicular extracts upon his own person were the real foundation of the modern science of internal secretory therapeutics. For years information on the numerous phases of the subject was indefinite and dis-associated. What the gland secreted and how the deficiency affected the disease was then but imperfectly known; still the adrenals and the thyroid and other organs gradually began to have a responsibility in regard to morbid conditions placed upon them, and these glands, obtained from animals, were used empirically in almost every conceivable condition.

Then followed what might be called a craze for organo-therapy. Almost every internal organ of the sheep or ox, from the brain to the testes, was removed and served with pharmaceutical skill in the form of desiccated powder, compressed tablets, or glycerine extracts. Doubt-less benefit was derived from the treatment, but soon much of it was discarded, although in France *opothérapie* is to-day as popular as ever it was.

A Recent Estimate of the Basis of Internal Secretory Therapeutics.—Italian physicians, next perhaps to the French in the activity of their investigations of this subject, have contributed much valuable information to the sum of our present knowledge. At a recent Italian congress* an official report was made and adopted, in which it is deemed established that the "endocrinous system"†—the internal secretory system—exerts an in-

* The Italian Society of Medicine at a special meeting held in Rome, October, 1912.

† The word "endocrinous" is incorrect. It should be "endocritic," but in deference to general usage the former term will be used throughout. See Glossary.

fluence on anomalies of growth, morphogenesia, and organic metabolism, on nutrition and inherent excitability of the nervous system, and on resistance to infections and intoxications, and also that it has a preponderating influence on the causation of dyscrasias and morbid temperaments. The equilibrium of the nervous system, the sympathetic in particular, is also regarded as maintained by the internal secretions. In nervous diseases *per se* they act probably as indirect or predisposing factors.

In commenting editorially upon this report the *New York Medical Journal* says[4]: "One cannot but be impressed by the vast field which the ductless glands have steadily invaded, in keeping with the conclusions announced nearly ten years ago in this country, that these organs were second to none in the body in their bearing upon physiology, pathology, and clinical medicine. . . . The array of disorders enumerated in the report in which the internal secretions are now known to take part is such that pathology bids fair to require a complete readjustment if its tenets are to harmonize with all established facts."

Charlatanism and Animal Therapy.—There is, unhappily, a tendency on the part of many physicians to look askance on the use of animal preparations other than those so well known and already mentioned. To many it still savours of quackery, for did not the immortal Pliny advocate the use of some fifty or more preparations from the hyæna for as many human ailments? and if so, why not limitless preparations from the whole animal kingdom for practically all the ills to which the flesh is heir? And do not many Chinese "physicians," whose ideas we scorn, still use such animal preparations as powdered deer's horn, hoof of a white horse, thigh of a grey horse, eyes of a tiger, etc.?

Unfortunately for the progress of scientific organotherapy, the important work of Brown-Séquard with testicular extract was immediately taken up with avidity by many astute quacks, and his suggested treatment was lauded to the world as the one sure cure for impotence and other conditions which are of such a nature as not only to influence the organs concerned, but also the credulity of the unfortunate sufferer. Thus the fundamental value of Brown-Séquard's work was in a measure discredited, although the professional reputation of those among the first to use this new method should not be permitted to belittle the fact that these medicaments have a very wide and increasing range of usefulness, that our knowledge of the subject is being put on a scientific basis, and that those physicians who do not appreciate this to the full are separating themselves from means to very encouraging ends.

The Scientific Establishment of Hormone Action.—As a result of the stimulus given by this pioneer work, however, many set themselves to unravel the intricacies of various phases of this vast subject, and among many important discoveries one stands out as epoch-making. This was the chemical isolation of the first endocrinous active principle in 1901, when the hormone of the adrenal medulla was given to the world by Takamine[5] of Detroit. How this substance brought about its remarkable action was only hinted, and it was left to Starling and his coworkers to determine the basis of the actual relations of the internal secretions in physiology.

The discovery of the principle of hormone action was brought about by the experiments of Bayliss and Starling[6] in the research laboratory of University College, London, in 1902. These gentlemen, in studying the then newly discovered enterokinase, proved that the presence of an

acid, or acid stomach contents, in a loop of small intestine was always followed by a secretion of pancreatic juice, and that this took place notwithstanding the careful destruction of all nerve channels. The details of the study and the action of the first-named hormone—*secretin*—will be found in Chapter V.

About this time, in the same laboratories, the so-called "mamma hormone" was demonstrated by Starling and his assistant, Miss Lane Claypon,[7] and it seemed necessary to propose a term to cover these chemical agents, or messengers, which, when carried by the blood, serve to co-ordinate the activities of certain remote organs. Starling therefore proposed the term "hormone," from the Greek ὁρμάω, "I arouse or excite," and in the decade that has passed the innumerable experiments have proved the soundness of this premise, and have established the hormones in therapeutics as well as in physiology.

Hormones are evidently definite chemical substances produced either with a special predestined action or as by-products in the normal cell catabolism, which serve to unite the complex of activities of the body into a functional harmony, both by means of chemical regulation effected through humoral channels, as well as, in certain cases, by means of reflex control exerted by the nervous system.

Starling's Conception of the Hormones.—One of Starling's earliest pronouncements on the subject is to be found in profoundly interesting and illuminating consideration of the chemical co-ordination of the activities of the body.[8] In this article the author refers to the excitatory substances (*Reizstoffe*), long familiar to botanists, which have a decided dynamic effect on the living cell. In this respect they present a close analogy to the

substances that form the ordinary drugs of our pharmacopœias. One cannot do better here than quote Starling's own words: "Since in the normal functioning of the body they [the hormones] have to be discharged at frequent intervals into the blood-stream, and carried onward by this to the organ on which they exercise their specific effect, they cannot belong to that class of complex bodies, which include the toxins, of animal or vegetable origin. We must therefore conceive the latter as substances, produced often in the normal metabolism of certain cells, of definite chemical composition, and comparable in their chemical nature and mode of action to drugs of specific action such as the alkaloids. This conclusion is borne out by the few investigations which have been made as to the nature of the chemical messengers in the case of certain well-marked correlations of function in the higher animals. In consequence of the distinctive features of this class of bodies, and the important functions played by them in the higher organisms, I have proposed to give a special name to the class—viz., *hormones*, from ὁρμάω, 'I arouse or excite.'"

This, then, is the beginning of hormone therapy, the scientific explanation of that system of animal medication so steadfastly believed in throughout the ages. The body, it would appear, manufactures its own drugs. These are supplied by the glands of internal secretion; and not only have they the power to correlate and co-ordinate the various bodily functions—such as pregnancy and mammary secretion, growth and sexual development, and so forth—but they also destroy toxins, and, further still, these hormones *control one another*. The essential importance of this will be emphasized more thoroughly in later chapters.

How close the earlier students were to the essentials of

the action of hormones is shown in a paper by Brown-Séquard and his assistant d'Arsonval,[9] published in 1891. They refer to these chemical substances in the following terms: "These special soluble products [of the living cell] enter into the blood and serve to influence, with this liquid as the intermediary, other cells or anatomical elements of the organism. As a result, the diversified cells of the economy are thus correlated with one another by means of a mechanism other than the influence of the nervous system."

Definitions of the Term "Hormone."—In a paper published nearly twenty years later, Howell[10] of Johns Hopkins University defines hormones as "those substances in solution which, conveyed from one organ to another through any of the liquid media of the body, effect a correlation between the activities of the organ of origin and the organ on which they exert their specific effect."

Starling's most recent statement embodying a definition of hormones was given in a discussion on the therapeutic value of hormones held by the Royal Society of Medicine.[11] He says: "By the term 'hormone' I understand any substance normally produced in the cells of some part of the body and carried by the blood-stream to distant parts, which it affects for the good of the organism as a whole. The hormones are thus the chemical means of correlation of the activities of different parts of the body. Their action may be either the increase or diminution of function, or the alteration of nutrition or rate of growth." He then proceeds to classify the hormonic actions into two classes, which he terms "the acute" and "the chronic." Typical examples of the former are secretin, carbonic acid, and adrenaline; of the latter, the thyroid, anterior pituitary, and luteal hormones. Star-

ling believes that the "chronic" class of hormonic reactions offers the best chances for therapeutic interference, as it includes the only definite instance of successful substitution therapy at present known—*e.g.*, the use of thyroid extract.

It seems quite evident that all the glands of internal secretion are active principally through the influence of the hormonic content of their secretion, and while several of these hormones have been extracted (secretin, *hypophysin*, *adrenalin*, etc.), it is still necessary to presume that they are present in suitably prepared extracts of the various organs; and that, because of their general stability and the fact that they are active in animals other than those in which they are produced, they may be used to bring about, in part at least, in man those co-ordinative activities which are their specific duties.

A Classification of Hormones.—Of course the action of the various substances usually called "hormones" is widely divergent, and, strictly speaking, they are not all entitled to be included in this class. Recently a suggestion was made with a view to the classification of these chemical messengers. At the Section of Physiology of the Seventeenth International Congress of Medicine a noteworthy paper on "A Proposed Classification of Hormones" was read by Sir E. A. Schäfer. He considers the term "hormone" not strictly applicable to every principle of the internal secretions, for the word implies excitation, while many of these principles really relax or inhibit rather than excite. He therefore suggested a generic name indicative of their drug-like action, and proposed the term "autacoid" (from *αὐτός* and *ἄκος*, "a remedy") for the entire group, subdividing these into "hormones," those that excite, and "chalones"

(χαλάω, "to relax"), those whose action is of an antagonist nature or inhibitory.

This tentative nomenclature has not yet been generally accepted, and it is likely that, just as the incorrect and inappropriate term "vaccine," to indicate a certain bacillary emulsion, is in everyday usage, so the word "hormone" will continue to indicate the active principles of the internal secretory glands which serve as chemical messengers to correlate the activities of the body, irrespective of whether they are excitants of positive activity —*e.g.*, stimulators—or excitors of negative activity—*e.g.*, inhibitors. Howell very rightly said in 1909 that it was likely that the term "hormone," like some ot the useful nomenclature of immunology, will be overworked.

The Present List of Known Hormones.*—By "known hormones" are intimated those principles the presence of which is presumed because of definite action caused by the organ producing them; they are not necessarily capable of isolation or even of standardization.

"The substances of known composition which may be regarded as playing the rôle of hormones are few in number, three or four at most, as follows: *First*, the carbon dioxide formed in the tissues, particularly in muscle during contraction. It seems agreed now that the carbon dioxide acts as the normal stimulus to the respiratory centre. When produced in the working muscles in such quantities as to raise perceptibly the carbon dioxide tension in the alveoli of the lungs and the blood of the pulmonary veins, the respiratory centre is excited to greater activity, and the excess above the normal contents is thereby removed; *second*, the adrenalin of the adrenal

* This list is taken from Howell's address before the Section of Physiology and Experimental Medicine, American Association for the Advancement of Science, 1910.

glands, which in some way, directly or indirectly, makes possible the full functional activity of the involuntary musculature of the body; *third*, the hydrochloric acid produced in the stomach, which stimulates the formation of secretin in the duodenal epithelium; and *fourth*, possibly the iodothyrin of the thyroid gland with its dynamogenic effect upon the neuromuscular apparatus of the body. In addition, there are a number of hormones of unknown composition which have been either proved or assumed to exist, and which are held responsible for certain well-known correlations of function. The pancreatic secretin formed in the epithelium of the duodenum or jejunum, which stimulates the flow of pancreatic secretion; the gastric secretin formed in the pyloric mucous membrane, which gives rise to the chemical secretion of gastric juice; a secretin formed in the duodenal epithelium, which stimulates the formation of intestinal juice in the following segments of the intestine; unknown hormones of pancreatic origin, which determine the absorption activity of the intestinal epithelium; vaso-dilator hormones formed in tissues in functional activity, and which have a specific effect upon the vessels of the functioning organ; a vaso-constricting and diuretic hormone formed in the posterior lobe of the pituitary body; a hormone controlling the growth of the bones and connective tissues produced in the anterior lobe of the pituitary body; a hormone controlling the oxidation of sugar in the body and produced in the cells of the islands of Langerhans in the pancreas; a hormone produced in the thymus, which controls possibly in some way the development of the reproductive organs; a vaso-constricting hormone formed in the kidneys; a hormone in the salivary glands, which controls the flow of water from the blood-capillaries in the glands; a hormone produced in the fœtus *in utero*, which stimulates the

growth of the mammary glands; a hormone in the ovary, which controls the growth of the uterus and the processes of menstruation; a hormone in the ovary, which controls the implantation of the fertilized ovum and the growth of placental tissue; a hormone in the testis, which initiates the development of the secondary sexual characteristics in the male; hormones of an indefinite number, produced in all the tissues and acting specifically upon the determinants in the gametes in such a way as to make possible the transmission of acquired characteristics."

A Comparison of Hormones and Enzymes.—The importance of the difference between hormones and ferments or enzymes must be emphasized. Enzymes are complicated chemical substances—unorganized ferments—which are capable of causing chemical changes in certain other substances without themselves being permanently changed in the process. Among these are such well-known substances as diastase, pepsin, trypsin, etc. These are invariably destroyed* by heat, and are capable of performing their function outside of the tissues. Hormones, on the other hand, are complex but evidently quite definite chemical substances produced in various cell-groups; their function is to provoke the production of enzymes and ferment action, and generally to act as excitants to numerous manifestations of physiologic activity. Hormones are carried directly into the blood, are quite stable, and can withstand a much greater degree of heat. A ferment consists of the product of the cell

* This is the general impression obtained from the current literature, but it seems that not all enzymes, at least, are "destroyed" by heat. Rather should we say that they are rendered inert by heat. Experimental confirmation of this is found in the consideration of the salivary glands in Chapter IV. It has been stated that enzymes are more stable than hormones, for they are not "used up" as are the hormones, but are "virtually indestructible," being used and re-used indefinitely. More proof of this is needed.

producing it, the proferment, *plus the hormone.* The proferment is not active until it has been influenced by the hormone, while the hormone itself is not influenced save only as it serves its work as a chemical messenger. (The reader's attention is directed to the glossary which forms Chapter XXXV. in the Appendix, in which the numerous terms directly or indirectly related to this subject have been explained.)

Starling has indicated that hormones belong to the crystalloid rather than to the colloid class of substances, and that they are therefore thermo-stable, and do not act as antigens when injected into the living animal. The stability of these substances and their resisting powers against ordinary heat differentiate them entirely from ferments and enzymes.

It must also be remembered that since there is an absence of antigen action when they are used in therapeutics, the body does not immediately attempt to destroy them as it would foreign substances; but as soon as they enter the blood-stream they are appropriated by the organ which they specifically excite, just as are those similar substances which it is desirable to replace or augment.

The Selective Action of the Hormones.—Perhaps more experimental work has been done with the first hormone —secretin—than with any other, because of the perfection of the present methods for separating it, and the comparative ease with which it is separated from the duodenal cells (see chapter on Secretin). It is quite reasonable to presume that the action of the hormones as a class is uniform, and, without offending the physiologists, we can take it for granted that the various hormones combine with certain uniform substances in the cells to produce the stimulus or substance which it is their func-

tion to produce. It seems to be well established that secretin is used up in the reaction that takes place between it and the proferments of the pancreas, stomach, liver, etc., and the present idea is that these enzyme precursors are activated by actual combination with the secretin, and that the hormone is a component part of the completed ferment.

The general action of hormones has already been briefly intimated. Undoubtedly a specific selective attraction is manifested by certain organs for the hormones which activate them; and it is quite reasonable to imagine the blood-serum as a far more complex solution than has hitherto been presumed, containing, in addition to its cells, salts, opsonins, and other related substances, scores of hormones at one time, each of which is appropriated by the cells of those organs which are specifically stimulated by it.

The Rôle of the Blood-Plasma.—Much of intense interest will be found in a series of articles by Harry Campbell, entitled "The Rôle of the Blood-Plasma in Disease," and published in the *Lancet* during the early part of 1907.[12] Campbell has very lucidly outlined the important part played by the blood-plasma, not only in every function of health, but practically in every condition of disease. He has very forcibly emphasized the importance of the work of the individual cell, and for convenience divides its activities into two parts—egoistic and altruistic. The former consists in the maintenance of the individual cell vitality; while the latter, possibly an entirely secondary function, consists in supplying the organism as a whole with certain service, such as control by the nerve cells, the production of ferments or hormones, and the elimination of toxins by gland cells, and the causation of motion as with muscle cells. This author

points out that the cell itself may be to all intents and purposes quite healthy and still gravely fail in its altruistic functions—a failure which, small though it may be, may suffice to disorganize the delicate hormonic balance of the body, either by permitting the presence of an excess of a certain substance, as, for example, is generally considered to be the case in Graves's disease, or by the lack of it, as in myxœdema.

With these facts in mind, we can consistently pass to a consideration of the fundamental principles of hormone therapy.

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CHAPTER II

THE FUNDAMENTAL PRINCIPLES OF HORMONE THERAPY

The Importance of the Metabolism in Disease—The Value of Hormones in Indefinite Metabolic Disorders—A Study Fruitful in Promise—The Range of Hormone Action—The Outside Control of Hormone Production—The Homostimulant Action of Organic Extracts—On the Dosage of Hormone Preparations—The Prospects of Hormone Therapy.

THE study of hormones and their use as factors in the stimulation or inhibition of certain functions of the body has arrived at a stage which reaches well beyond the laboratory of the physiologist; and although experimental physiology is destined to throw much more light on this subject, in certain phases of it, at least, its application in clinical therapeutics is already established on a firm basis.

The Importance of the Metabolism in Disease.—To apply these fundamentals successfully in general practice, it is essential to appreciate to the full the importance of the rôle that metabolism plays. We have been accustomed to consider certain diseases in a class by themselves, and to call them "disorders of metabolism," and by this segregation we have been led to overlook the fact that the chemistry of the body is of equal importance in practically every other disease. One should also have a fair knowledge of pathologic anatomy, or, if this is not feasible, at least of the pathologic physiology of various glandular organs in certain diseases.

Fortunately, the extensive experimental work necessary to secure such information has been well done by numerous interested investigators of unquestioned reputation and excellent standing. One need only refer to the voluminous literature published during the past few years to become fully convinced that not only are many diseases accompanied by changes in structure and function of certain secretory organs, but also that the administration of corresponding gland substances has proved well worthy of further study and clinical application. It must be emphasized that one cannot always expect a definite disease picture to respond favourably to a correspondingly definite organotherapeutic remedy; but among a number of quite definite disease entities which have been shown by experience to be influenced by hormones are apepsia and the indigestions generally, pancreatic insufficiency, asthma, intestinal stasis and atonia, utero-ovarian disorders, as well as the numerous conditions amenable to thyroid, pituitary, and adrenal medication.

The Value of Hormones in Indefinite Metabolic Disorders.—On the other hand, there are not a few very indefinite, but none the less well-marked, symptoms-complex which have been found to be amenable to this form of therapeutics, and among them we must not overlook neurasthenia, suboxidation, certain mental disorders, malnutrition, and tuberculosis. In numerous other states not strictly classed as "disease," hormones may form a useful adjunct method of treatment and a means of increasing the necessary normal stimuli. Among these are pernicious vomiting of pregnancy, the act of parturition, lactation, uterine involution, suboxidation, obesity, deficiency in gastro-intestinal function, etc.

The value of thyroid extract in myxœdema is beyond question. It is a specific. This being the case, now that

we can really augment a diminished, or can supply an absent, hormone, have we not accomplished a direct curative service that stands high above our usually indirect and more or less haphazard methods of treatment? If, then, it is possible to secure from animals those substances which in the normal course of events would have accomplished certain physiologic services in these animals, and by introducing them into the human system, thus accomplish for the patient what they were intended to do for the animal, is there not a very good ground for a more general study of hormone therapy, and a broader application of this idea in every phase of general practice?

Unfortunately, not every hormone-bearing preparation is as uniform in its action as thyroid extract is in myxœdema, and where in one case excellent results may be obtained from a product of this character, in another we find very mediocre changes. We are still in the dark as to the explanation of many facts regarding these matters. We cannot tell exactly why the results vary so greatly, but it seems clear that the effects of a hormone given as a therapeutic agent are in proportion to its power to stimulate or inhibit the corresponding parts of the endocrinous system, and evidently the responsiveness of these various organs differs greatly in different individuals. "It is also probable that one hormone may, to a certain extent, be able to supplement or replace another of similar but not identical properties. These points serve to illustrate how much less we know about the hormones than we do about the ferments secreted by the digestive glands, and how further knowledge of the physiological action of the hormones will enlarge their sphere of action as therapeutic agents."[1]

Furthermore, we now have a class called "diseases of

the internal secretory organs " in which definite pathologic changes have been found in certain of these glands, as in Addison's disease, goitre, acromegaly, etc. We must not allow ourselves to overlook the minor and intangible disorders of the internal secretory organs, which, because of their insidiousness, often escape attention, although, because of their comparatively greater frequency, they are of equal or even greater importance to the general practitioner than are the major conditions, the presence of which is patent.

This is at once the most promising and most complex of the prospects before us, and the more it is studied the greater will be the encouragement to delve deeper into the mysteries of this fathomless subject.

We have already seen how for over fifty years it has been known that certain glands have a direct as well as a remote influence upon other glands and upon numerous functions of the body, but until very recently the substances responsible for this influence have been quite hypothetic. They had not been isolated and named, although evidence of their presence was plentiful. Consequently, when the practice of opotherapy was first begun, the glands themselves were administered *in toto ;* later glycerine extracts and dried extracts were used. Naturally much therapeutically useless material was given in this way, and not infrequently such extracts contained antagonistic substances which interfered in a varying degree with the desired therapeutic action. As yet we have learned little of the methods of preparing hormones in a pure state. Some have been isolated, and of these at least two—the adrenal and posterior pituitary hormones—are now of known chemical form, the former even having been made synthetically. Our knowledge, however, has increased our capacity to produce active

preparations, and recourse to the vacuum-drier has facilitated this work very much.

A Study Fruitful in Promise.—While the hormones are still on the verge of our knowledge, many do not appreciate their value through quite pardonable ignorance. Since their range of activity is as yet known only in part, the part is undervalued by many because our knowledge of it is admittedly incomplete. At a new departure that revolutionizes our present methods we hesitate, because we are loath to let go the notions so thoroughly ingrained in our medical constitutions.

No one who has used hormones for any length of time, and who is in a position to appreciate their specificity and value, can deny the extreme importance of this phase of therapeutics. Surely, as Dr. Leonard Williams has so well said[2]: "This is a subject of inquiry as fascinating as any in the whole range of medicine, and as fruitful in promise as any in the whole range of therapeutics."

The Range of Hormone Action.—To the student of practical therapeutics an outline of the availability of hormone action will be of interest. There are several different ways in which the hormones may render therapeutic service:

1. Substitution therapy: by supplying missing hormones the definite loss of which is known to be due to destructive lesions or congenital absence of an organ. For example, as in hypothyroidism, where the thyroid treatment actually replaces a secretion.

2. Supplementary therapy: by augmenting directly or reflexly a presumed deficiency, due either to an increased physiological demand or to a decreased hormone output. This includes both the hormone and the chalone action, as exemplified respectively by the luteal treatment of amenorrhœa and the pancreas treatment of glycosuria.

3. Specific physiological therapy: by producing a definite physiological influence which is indicated, but is not due to any change in the normal hormone-production of the patient, as in the use of infundibular extract for stimulating uterine contractions during labour, or of the angiotonic and styptic action of adrenaline.

4. Empirical application: a strictly unscientific but nevertheless sufficiently useful phase of hormone therapy, which produces results in a manner which is clinically evident but more or less unexplainable from the strictly scientific basis, as in the pituitary treatment of functional ovarian disorders, the parathyroid treatment of paralysis agitans, the thyroid treatment of rheumatic arthritis, or the pluriglandular treatment of "run-down conditions," etc.

The Outside Control of Hormone Production.—Another most important feature of the broad usefulness of hormones in normal physiology, as well as in their therapeutic application, is the fact that, in addition to their specific activating powers, hormones control their own production as well as one another. It is equally true, although by no means as extended in its possibilities of application, that the inhibitory or antagonistic action of certain hormones—or the "chalones," as they may yet be called—is available in the control of certain conditions in which the production of hormones by an organ is an excess of the needs of the body, and is hence a deterrent to the physiological harmony. This is best illustrated by the conditions known as "hyperthyroidism" and "hyperovaria."

This is a most important phase of hormone therapy; for we must remember that when a certain secretion is deficient, not only have we the results of this deficiency to deal with, but we have also the baneful effects of an un-

controlled antagonistic secretion. This "hormone balance" is a most important factor in medical treatment, and one that is very frequently overlooked. It seems advisable to lay special emphasis on the intricacies of these interactions, and the subject is therefore considered in a chapter by itself.

The Homostimulant Action of Organic Extracts.—One of the most important advantages of hormone therapy is dependent upon the influence which hormone-bearing extracts have upon the organs to which they correspond. This is so general that it seems to be an invariable occurrence. Hallion[3] was apparently the first to refer to this influence, and the following axiom has been called "Hallion's law": 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.

Here, then, is one of the fundamentals of this method of treatment; and while it is manifestly useless to hope to regenerate an organ which is totally destroyed, it has been proved, again and again, entirely possible to regenerate that part of the gland which is not yet beyond the hormone stimuli, and even to cause a hypertrophy of the tissue thus regenerated, thereby restoring a measure of its former usefulness.

On the Dosage of Hormone Preparations.—Since hormones are beginning to be used extensively as drugs, the subject of dosage is naturally an important one. As the manifest service of a hormone is not to supply nutritive material to the cells, but to stimulate them to certain functions, a very small amount suffices to cause the desired results. The majority of hormones are innocuous, and the inert material frequently associated with them

when used in the form of animal extracts is non-toxic. There are, however, several exceptions to this rule; the dose of thyroid extract must be very carefully regulated, and extract of the prostate gland is quite toxic. Very minute doses of adrenaline and infundibulin are used, and their influence should be always carefully watched; but, generally speaking, extracts of such organs as the duodenum, spleen, liver, pancreas, ovary, testicle, mammæ, etc., are not dangerous, and the dosage is based rather upon experience than upon careful toxicologic experiments.

The Prospects of Hormone Therapy.—If, then, it is possible successfully to influence the cell-workings of various organs by means of substances procured from other animals, the possibilities open to us are immense, and progress to the ultimate control of many complicated conditions is limited only by the capacity of the pharmacist to produce, in convenient form and at a reasonable price, satisfactory preparations from those various animal organs.

There is a genuineness in the enthusiasm of many students of this subject that many less interested individuals have not appreciated. The prospect of results in this field of research are positively enormous, and as our knowledge broadens and the facts become more generally known, many of these possibilities will become actualities, and available in the everyday routine of any physician who is willing to apply them.

This, all too briefly outlined, is the present position of hormone therapy. That it opens up a new pathway in therapeutics is undoubted. It explains in many respects the action of the older drugs, and affords a solid groundwork for future methods of treatment. It would seem of the utmost importance, then, that practitioners should

become thoroughly acquainted with its many ramifications, and with this object the author has collated here many recent opinions and findings on this highly important subject.

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CHAPTER III

THE HORMONE BALANCE

The Intercellular Equilibrium—The Control of Nutrition—A Possible Relation of the Internal Secretions to Cancer—Glycosuria : An Illustration of a Disturbed Hormone Balance—The Hormone Control of Carbohydrate Metabolism—The Thyroid Control of the Hormone Balance—The Influence of the Ovaries—The Kinetic System—Hormone Stimulation of Muscular Activity—A Diagram showing the Relations of the Endocrinous Organs—The Psychic Control of Endocrinous Action—A New Idea in Organotherapeutic Preparations—The Loss of the Hormone Balance—The Modification of Disorders of the Hormone Balance.

The Intercellular Equilibrium.—In the body every motive force is balanced by a retarding force, and this nice equilibrium is quite essential to the proper regulation of the numerous cellular functions. Should one or other of two factors gain the ascendency, disorganization may be expected at once, and the extent of this disturbance can hardly be confined to the single area in which it is initiated. This is evidently what happens in diabetes, myxœdema, acromegaly, ovarian insufficiency, and numerous other conditions related to the internal secretory system. If we are able partly or wholly to restore that balance by the addition of a suitable agent in the form of an animal extract or hormone, we shall have assisted Nature in a very effective and helpful manner.

Numerous writers have considered the close interrelation between the internal secretions, and have demonstrated that certain of these secretions are synergists,

while others are antagonists.[1] Bearing in mind the altruistic function of the cell mentioned in the first chapter —that function which influences its near or remote neighbours — the importance of the hormone equilibrium may be faintly appreciated.

The Control of Nutrition.—The principal function of the hormones is the maintenance of cellular activity of the control of bodily nutrition. As the subject becomes more thoroughly studied, we may expect to find out more definitely how this influence is exerted. At present we must be satisfied to believe that the hormones are far more important factors than the trophic nerves, although doubtless a combination of their activities is essential.

This fact is an important underlying reason for the variations in susceptibility to disease, and it is not too much to state that the condition of the hormone balance is of paramount importance in the maintenance of health. It is quite likely, moreover, that the modification of certain chronic dyscrasias by dietetic and hygienic measures is specifically caused by the influence of these measures upon the activities of the ductless glands. Some interesting experimental work gives weight to this suggestion, and seems to show a connection between the internal secretory activities and cancer.

A Possible Relation of the Internal Secretions to Cancer.—Following the experiments of Hunt[2] in the Government laboratories in Washington, which showed that certain drugs and diets were capable of equally stimulating or repressing the activities of the thyroid gland, it has seemed that dietetic regulation may influence the growth of certain tumours. Some very interesting work has been done in this connection by Osborne and Mendel,[3] which, while beside this subject, bears a certain relation to some interesting experiments at the American Oncologic Hos-

pital in Philadelphia. Sweet, Corson-White, and Saxon[4] have shown that the diets suggested by Osborne and Mendel have a decided influence upon the development of transplanted tumours in animals; and still more interesting than this is the fact that tumours transplanted into animals which had previously been deprived of certain internal secretions, such as that of the gonads, showed that the animal was rendered more susceptible since the frequency of the establishment of the tumour growth and the rapidity of its growth was noticeable. In this connection it is interesting to recall that cancer is essentially a disease of that period of life when certain of the ductless glands lose their normal function, this loss entailing related changes in the whole chain of interrelated functions of the ductless glands.[5] Perhaps it is suggesting too much to say that the ductless glands are responsible for the condition of the body which permits the growth of cancer cells, or that by applying the fundamentals of organotherapy we are likely to be able to control this disease; but such facts as these seem very pregnant, and it is by no means impossible that future study will show that the hormones may be very intimately concerned in the prevention and cure of this dread disease.

Glycosuria: An Illustration of a Disturbed Hormone Balance.—Much has been added to our knowledge of the hormone balance by the study of several diseases in which hormone action and interaction are intimately concerned. Prominent among these is diabetes, one form of which now seems definitely to be classed as a disorder of certain of the organs concerned in the maintenance of the hormone balance. From the numerous experiments which have been made, we know that there is a close relationship between the internal secretions of the pancreas and thyroid. They oppose one another, and it seems to be

established that "in hyperthyroidism the function of the pancreas is depressed and alimentary glycosuria is easily brought about. On the other hand, in atrophy or hyperplasia of the thyroid gland, the pancreatic powers are increased, and patients suffering from these disorders —for instance, myxœdema—can take large quantities of glucose without the slightest glycosuria. . . . The thyroid also can be influenced by the pancreas, and so we are not surprised to find that the moment the pancreas is ablated, the thyroid function gains the upper hand."[6]

The pancreas also "acts as a brake upon the sugar-producing mechanism." This was first emphasized by Opie, whose work and its importance is more fully referred to in the chapter devoted to the pancreatic hormone, and later quite conclusively proved by Eppinger, Rudinger, and Falta. They also showed that the adrenal bodies play an important part in the glycosuric-complex, as the chromaffin hormone—the hormone produced in the adrenal chromic-acid-staining cells—regulates the excitability of the sugar-producing mechanism of the liver. This is directly antagonistic to the work of the pancreas, as it is one of stimulation. Von Noorden[7] says: "Adrenalin gives a rapid expulsion of glycogen from the liver, and glycosuria results. . . . A moderate dose of adrenalin produces a glycosuria lasting for some hours; after that, normal conditions are restored. . . . If injections are repeated several times, glycosuria does not reappear. A much larger dose of adrenalin is required to produce sugar in the urine. . . . An inhibition of the action of adrenalin may be explained by supposing that the pancreas was taken by surprise by the first stimulating dose, and consequently could not prevent the disturbances of sugar control; but the repetition of the stimulus puts the pancreas into a strong defensive position, and a stop is

put to the disturbance in the regulating mechanism produced by the adrenalin."[8]

The pituitary evidently is concerned in the metabolism of carbohydrates, for disturbances of pituitary function have frequently, as one of the associated symptoms, the presence of a greater or less degree of glycosuria. The parathyroids also stand in a metabolic relation to the pancreas, and certain experiments have been made to show that they are related to a number of the other internal secretory organs. It may be stated here that parathyroid ablation weakens the functions of the pancreas and favours glycosuria, proving that their action is antagonistic to that of the thyroids.

The Hormone Control of Carbohydrate Metabolism.—Von Noorden[9] has illustrated his views regarding the control exercised by the various hormones upon one another in the intricacies of carbohydrate metabolism by a diagram, which, with the permission of this distinguished authority, is reproduced on p. 33.

His own description of this diagram follows:

The dotted lines indicate "nervous paths," the continuous lines "blood paths"; the arrows show the direction of the stimulus; and the plus or minus signs behind them show whether the stimulus increases or inhibits the power of the organ which is influenced.

The normal metabolism of the carbohydrates is concerned only with Paths I., II., and III. *Path I.* shows that material, inciting an increased activity of the sugar-forming mechanism, streams up from the intestine to the liver. This path in diabetes corresponds to the "alimentary factor" in glycosuria. We can, at will, control the stimuli passing up by this way. The conscientious carrying out of this is the aim and object of diabetic cures.

Paths II. and III. show the action of the metabolic processes as a whole. Along Path II. are transmitted the requirements of the tissues (especially the muscles), and their extent corresponds to the amount of sugar formed and exported by the blood (Path III., hepatic vein, heart, and arteries). The total stimulus transmissal by Path II. can also, to a certain extent, be voluntarily controlled. It can be diminished by excluding everything which markedly increases the total production of

calories (such as heavy muscular work, loss of heat, abundant food, high protein diet). That these are the factors which increase the production of calories and at the same time the formation of sugar has already been noted; and we make use of this knowledge to achieve our aims in the treatment of diabetes.

By *Paths A and B* the influences are sent from the two most important and powerful controllers, which govern the sugar factory, the sensitizing suprarenals (A), and the calming pancreas

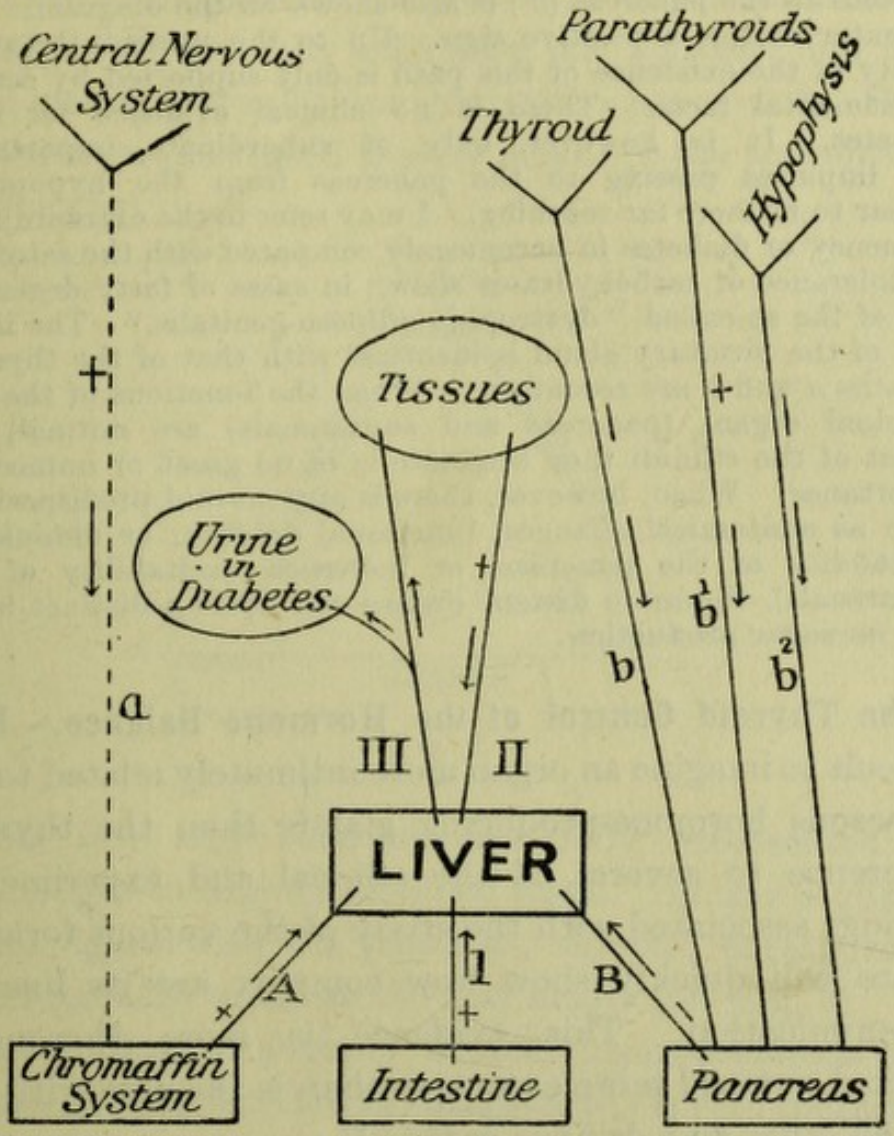


FIG. 1.

(B). Along *Paths a and b* indicate the active influences by which the functions of the controlling organs can be increased or diminished. Along Path *a* pass the nervous impulses. It is along this path that the piqûre of Claude Bérnard exerts its effects, and psychical disturbances obtain their influence over the sugar production of diabetes. There may also exist other paths which influence the production of adrenaline, and consequently that of sugar also; I refer to the over-activity of the suprarenals and the

hypertension developed in chronic nephritis. But there is so much uncertainty surrounding this and other questions that I have only suggested in the diagram the possibility of other paths than that of the sympathetic.

Path b indicates the certain relationship between the thyroid and the pancreas. The indicator on this path carries a negative sign to show that the internal secretion of the pancreas is not increased, but inhibited by the thyroid. A path from the parathyroids to the pancreas (*b'*) is also shown on the diagram. The indicator carries a positive sign. Up to the present the probability of the existence of this path is only supported by certain experimental facts. There is no clinical evidence for it in diabetes. It is, however, only of subordinate importance. The impulses passing to the pancreas from the hypophysis appear to be more far-reaching. I may refer to the extraordinary frequency of diabetes in acromegaly compared with the astonishing tolerance of carbohydrates shown in cases of fatty degeneration of the so-called "dystrophia adiposo-genitalis." The influence of the pituitary gland is identical with that of the thyroid.

Paths *a* and *b* are secondary. When the functions of the two principal organs (pancreas and suprarenals) are normal, the extent of the stimuli they originate is of no great or immediate importance. When, however, there is any morbid predisposition (such as anatomical changes, functional debility, or diminished excitability of the pancreas, or increased excitability of the suprarenals), the more distant organs can exert a distinct influence on sugar production.

The Thyroid Control of the Hormone Balance.—It is difficult to imagine an organ more intimately related to the numerous hormone-producing glands than the thyroid. Reference to several of the clinical and experimental findings associated with the study of the various forms of goitre will quickly show how complex are its lines of communication. This evidence is more thoroughly worked out and more extensive than is the case with any of the other endocrinous organs.[10]

As we have just seen, the thyroid is an antagonist to the pancreas, and in this direction, at least, a complement to the adrenals. Fränkel[11] has shown that in Graves's disease the amount of adrenaline in the blood is increased several hundred per cent., and others have concluded that the thyroid stimulates the adrenal medulla. Ep-

pinger, Rudinger, and Falta[12] have performed numerous experiments involving excision of the thyroid and of the pancreas, as well as the administration of glandular preparations, and, in addition to their conclusion regarding the antagonism of the pancreas to the thyroid and adrenals just mentioned, they also found that the adrenals and thyroids mutually stimulate one another, and that these glands mutually antagonize the pancreas.* These writers have illustrated this by means of the accompanying diagram:

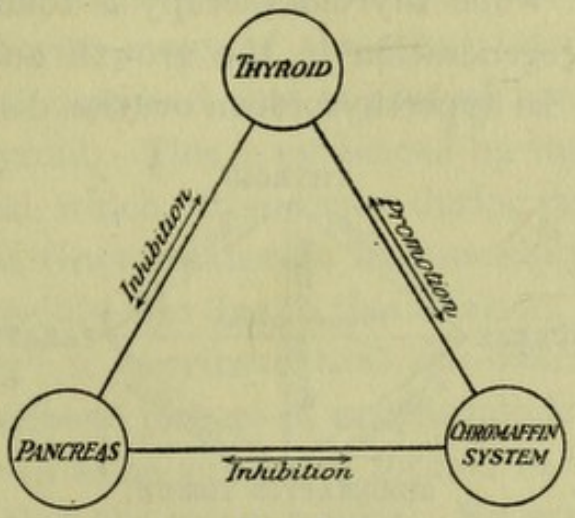


FIG. 2.

This has also been schematically represented by Cammidge[13] in slightly modified form. He uses a quadrilateral figure with the pancreas, thyroid, parathyroids, and chromaffin tissue at the four angles (see Fig. 3).

The findings at autopsy of many myxœdematous individuals have shown that thyroid atrophy is very frequently accompanied by pituitary hypertrophy, and the general consensus of opinion favours the view that the thyroid normally has an inhibitory influence upon the pituitary,

* This may be a reason why the pancreas is said to be six or seven times larger than the necessities of its normal production of external enzyme-bearing secretion actually require—it has such a vital position as a check to these important endocrinous glands. It may also be an explanation of the frequency of alimentary disorders in conditions of thyroid or adrenal excess.

especially its posterior lobe, and that the hypertrophy just mentioned is due to a partial or complete removal of this check.

More remarkable still is the relation of the thyroid to the gonads. Chief among the clinical manifestations of hypo- and hyper-thyroidism are disturbances in the reproductive glands. In myxœdema sex depression is very frequent, in men lack of development or impotence being the result. In women amenorrhœa and ovarian atrophy are common, while thyroid therapy is found to cause a remarkable regeneration in the growth and activity of the gonads. In hyperthyroidism ovarian disturbances are

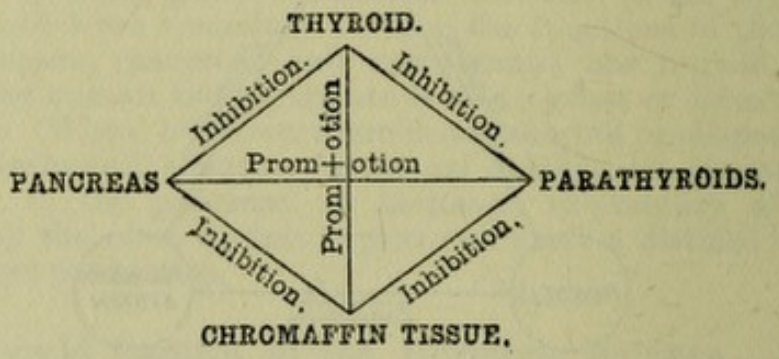


FIG. 3.

almost invariably found, Rogers[14] believing that "disturbances of menstruation with large and tender ovaries always occur in Basedow's disease." All ovarian involvements, however, are not identical, for in some cases amenorrhœa has been found, but dysmenorrhœa and menorrhagia are much more frequent. It is generally conceded that the thyroid stimulates the gonads and is an important factor in the establishment and furtherance of sexual activity.

Two other glands, or sets of glands—the thymus and the parathyroids—are unquestionably intimately connected with the thyroid. Their relationship is discussed in the chapters dealing with these respective subjects.

The Influence of the Ovaries.—Ott[15] has stated that: "Just as glands with an external secretion concur in taking up the work not accomplished by the others and unite in the perfection of the products to be brought forth, in a similar way the glands with an internal secretion concur in the metabolites to be produced; a sort of physiological balance is maintained between the activities of the different glands in the wilderness of metabolism." There are several hormones produced by the reproductive organs, and they have a close interrelationship with one another and with many of the other internal secretory organs. It is supposed that the luteal hormone antagonizes the thyroid. This is evidenced by the enlargement of the thyroid, which often occurs during pregnancy; and the fact that Graves's disease is essentially a disease of women is possibly also due to this relation.

Mannaberg[16] is convinced that the ovaries play some part in the clinical picture of exophthalmic goitre. This may be due to some substance formed in the ovaries in such a way that the goitre results. By exposures to the Röntgen rays, the source of this substance in the ovaries is dried up, and the thyroid is permitted to resume its normal activity. In ten cases in which he has applied this measure a favourable influence was manifest on all the symptoms except enlargement of the gland. He does not call it a cure in any case, as the pulse is still usually unstable. It is possible that a course of thyroid treatment might advantageously supplement the radiotherapy. In eight of the ten cases the patients gained from 2·3 to 21 per cent. in weight. In one case the exophthalmos completely subsided, and in the others there was no change. The most striking improvement was subjective; nearly all the patients felt entirely well.

This same hormone is in relation with both the adrenals

and pituitary body, for Schenk has shown that the removal of the ovaries in rabbits causes adrenal hypertrophy, and Mayer, Alquier, and others note that ovariotomy causes an increased pituitary function. The sexual glands are also closely related to the thymus, as evidenced by the fact that persistent thymus is usually found in individuals in which the sexual organs are undeveloped, and, further, the thymus is persistent in eunuchs. On the contrary, removal of the thymus in certain animals retards the growth of the generative glands.

The hormone produced in the mammæ is in close relationship with the generative organs, and the "mamma hormone" produced in the fœtus and placenta stimulates the growth and functioning powers of the breast. The production of the ovarian hormone at the commencement of menstruation serves a similar but less complete purpose. On the other hand, the hormone produced in the mammæ has a reserve action upon the ovaries and uterus, as will be evidenced in the clinical experiments with extracts of this organ, referred to in greater detail in the chapter devoted to this subject.

The Kinetic System.—As a result of his assiduous study of shock, blood-pressure, energy production, and the mechanism of the regulation of the functions of the body, Crile,[17] of Cleveland, has recently summarized his conclusions in a communication to the Cleveland Academy of Medicine. He brings evidence to support his view that there is a "kinetic system" which controls the production, storage, and output of energy.

How intimately this department of the bodily activities is connected with the hormone-producing organs, and how dependent it is upon the hormone balance, will be evident from the following paragraphs, which are taken from the introduction to Crile's most interesting mono-

graph: "The self-preservation of man and kindred animals is effected through mechanisms which transform latent energy into kinetic energy to accomplish adaptive ends. Man appropriates from environment the energy he requires, in the form of crude food, which is refined by the digestive system; oxygen is taken to the blood and carbon dioxide is taken from it by the respiratory system; to and from the myriads of working cells of the body food and oxygen and waste are carried by the circulatory system; the body is cleared of waste by the urinary system; procreation is accomplished through the genital system; but none of these systems are evolved primarily for the purpose of transforming potential energy into kinetic energy for specific ends. Each system transforms such amounts of potential into kinetic energy as are required to perform its specific work; but they do not transform latent into kinetic energy for the purposes of escaping, fighting, pursuing, nor for combating infection. The stomach, the kidneys, the lungs, the heart strike no physical blow; their rôle is to do certain work, to the end that the blow may be struck by another system evolved for that purpose. I propose to offer evidence that there is in the body a system evolved primarily for the transformation of latent energy into motion and into heat. This system I propose to designate *The Kinetic System*.

"The kinetic system does not directly circulate the blood, nor does it exchange oxygen and carbon dioxide, nor does it perform the functions of digestion, urinary elimination, procreation; but though the kinetic system does not directly perform these functions, yet it does play indirectly an important rôle in each—just as the kinetic system itself is aided indirectly by all the other systems.

"Among the organs in the kinetic system are the brain, the thyroid, the adrenals, the liver, the pancreas, and the

muscles. The brain is the great central battery which drives the body; the thyroid governs the conditions favouring tissue oxidation; the adrenals govern immediate oxidation processes; and the muscles are the great converters of latent energy into motion and heat. . . . Adrenalin alone, and thyroid extract alone, and brain activity alone, and muscular activity alone, are capable of causing the body temperature to rise above normal. The functional activity of no other gland of the body alone, and the secretion of no other gland alone, can cause a comparable rise in body temperature—that is, increase functional activity; and no active principle derived from the kidney, liver, stomach, pancreas, hypophysis, parathyroid, spleen, intestines, thymus, lymphatic glands, or bones can, *per se*, cause a rise in temperature comparable to the rise that may be caused by the activity of the brain, or the muscles, or by the injection of adrenalin or thyroid extract. Then, too, when the brain, thyroid, adrenals, or muscles are eliminated, the power of the body to convert latent into kinetic energy is impaired or lost. I shall offer evidence tending to show that an excess of either internal or external environmental stimuli may modify one or more organs of the kinetic chain, and that this modification may cause certain diseases. For example, alterations in the efficiency of the cerebral link yields neurasthenia, mania, dementia; of the thyroid link —Graves's disease, myxœdema; of the adrenal link—Addison's disease, cardiovascular disease."

Without a doubt this theory will be assailed, as all theories have been and will be; but there seems to be no ground for disputing the breadth of what was termed, and not so long since either, the "hormone theory," nor can one deny the extent and reasonableness of the system of therapeutics which has been built upon this "theory."

Hormone Stimulation of Muscular Activity.—Elsewhere reference will be found to the frequency of myasthenia as a symptom of endocrinous disturbances, and from the observation by Brown-Séquard of the dynamogenic effect of testicular extract, not a few experimental and occasional clinical investigators have demonstrated to what an extent the ductless glands influence the neuromuscular system. Markeloff[18] has carried out numerous experiments on dogs, and has determined the comparative effects of various endocrinous extracts. In addition to a number of commercial preparations he used freshly made glycerin extracts, and as a result of his deductions he has grouped the more important ductless glands into two classes—viz., those which stimulate muscular activity—the thyroid, testicles, pituitary body and adrenals; and those which depress muscular action—the parathyroids, pancreas, and thymus.

This information has been turned to good therapeutic advantage, and is more fully discussed in the study of pluriglandular extracts (Chapter XXX.).

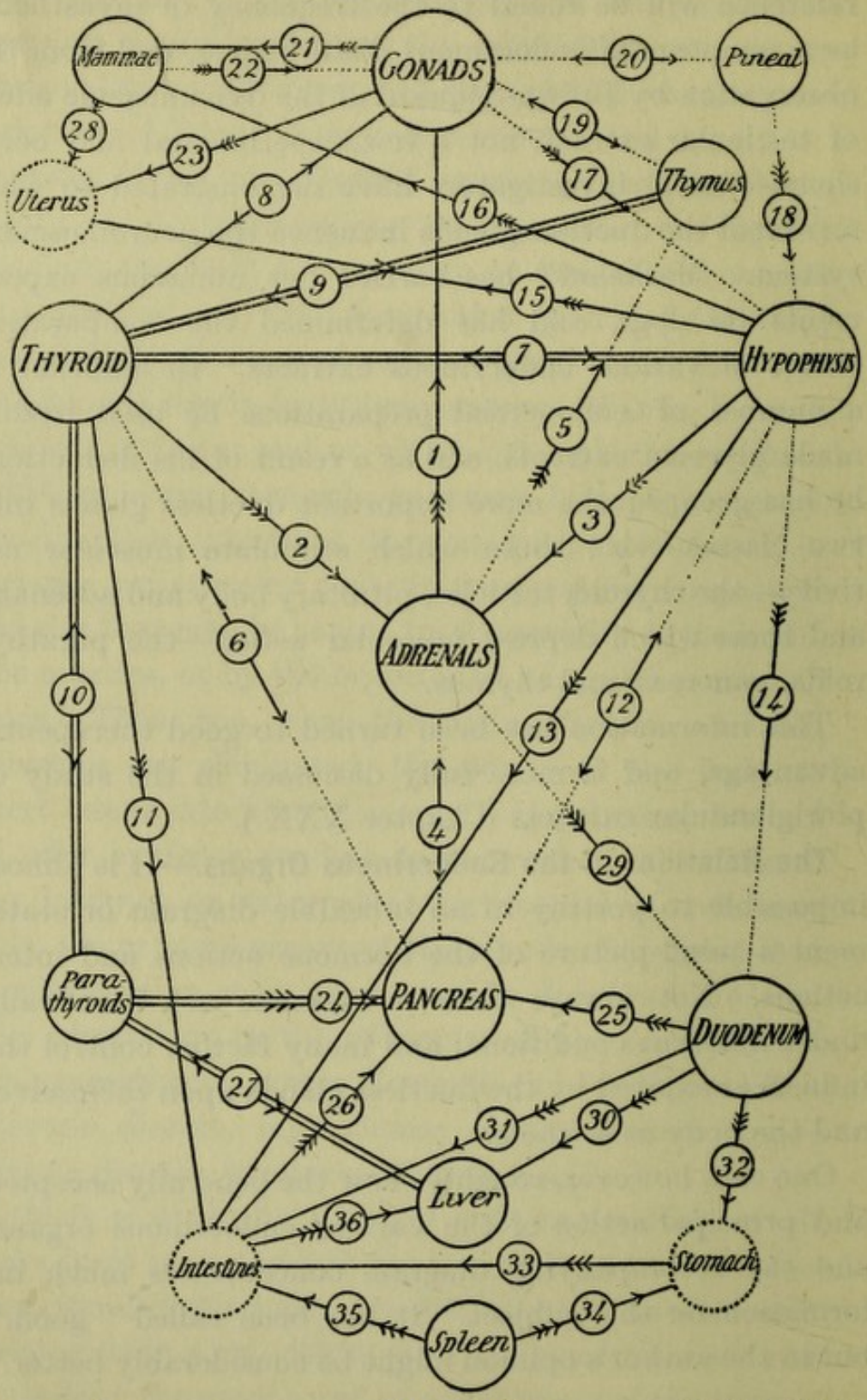
The Relations of the Endocrinous Organs.—It is almost impossible to portray in an inflexible diagram or statement a mind-picture of the hormone actions and interactions. Not always does a hormone act identically under different conditions; and many factors control the influences exerted by the ductless glands upon themselves and the body as a whole.

One can, however, roughly show the generally accepted and principal action of the various endocrinous organs, and the accompanying diagram concentrates much information on this subject. It has been called "good," but in the author's opinion might be considerably better.*

* Criticisms of this diagram with a view to rendering it more complete and less complex will be appreciated by the author, who may be addressed in care of the publishers.

THE RELATIONS OF THE ENDOCRINOUS ORGANS

(Schematically arranged)



= Co-operation. —— = Stimulation ..... = Antagonism.

FIG. 4.

KEY TO THE DIAGRAM OPPOSITE.

The ADRENALS seem to work in harmony with, and are stimulated by, the thyroid (2) and hypophysis (3), and are antagonists to the pancreas (4), especially in the control of sugar combustion. They also inhibit the thymus (5), and, perhaps, secretin (29). The cortex stimulates the gonads (1).

The THYROID stimulates the gonads (8), but may be also reciprocally stimulated by them. It has a co-operative relation with the hypophysis (7), and is closely but indefinitely associated with the thymus (9) and the parathyroids (10). It stimulates the adrenals (2), inhibits the pancreas slightly (6), and an excessive secretion stimulates the intestine (11).

The HYPOPHYSIS (posterior lobe), experimentally at least, stimulates the smooth muscle of the uterus (15) and intestine (13). It is co-operative with the thyroid (7), and is said by some to act vicariously for it. It stimulates the mammæ (16), but is slightly antagonized by the gonads (17) and the pineal (18). There is a mutual antagonism between it and the pancreas (12), and it also supplements, in a degree, the adrenals (3).

The GONADS check the pituitary (17), pregnancy (ovarian rest) or castration causing increased pituitary activity. They depress the thymus (19), for by their commencing action cause thymus retrogression. They are reciprocal with the adrenal cortex (1), are intimately related with the thyroid (8), being usually stimulated by it, stimulate the uterus (23) and mammæ (21), and, paradoxically, are during mammary activity antagonized by them (22).

The PANCREAS controls (and is controlled by) the adrenals (4), and in this connection is assisted by the parathyroids (24). It seems to be inhibited by the thyroid (6) and the hypophysis (12). Its stimuli come from the duodenum (secretin) (25), and, perhaps, the intestine (26).

The PINEAL inhibits the development of the gonads (20), and there is a degree of antagonism between it and the hypophysis (18).

The THYMUS inhibits the gonads (19), and *vice versa*. The evidence regarding its relation to the thyroid is somewhat contradictory; it is often stimulated by hyperthyroidism, and thyroidectomy often causes thymus hypertrophy (9). It is also inhibited by the adrenals (5).

The PARATHYROIDS are said to co-operate with the pancreas (24) and the liver (27). In a rather indefinite manner they are intimate with the thyroid (10).

The MAMMÆ are stimulated by the hypophysis (16) and corpora lutea (21), but they antagonize the ovaries proper (22) and the uterus (28).

The UTERUS is not generally conceded to be an endocrinous organ, but it may be experimentally stimulated by the hypophysis (15). The gonads stimulate its growth (23), and it is inhibited by the mammæ (28).

The LIVER is stimulated by the duodenum (secretin) (30) and intestine (36), and is stated to work in harmony with the parathyroids (27).

The DUODENUM (secretin) activates the pancreas (25), the liver (30), the intestine (31), and perhaps the stomach (32). Its work is inhibited by the adrenals (29) and hypophysis (14).

The INTESTINE stimulates the liver slightly (36) and pancreas (26). Its muscular activities may be stimulated by the spleen (35), the hypophysis (13), and slightly by the thyroid (11). It may be assisted by the stomach (33).

The SPLEEN is stated to have an activating power upon the work of the stomach (34) and digestion generally. It is also supposed to furnish a stimulant to the intestine musculature (35).

The STOMACH may activate the intestine (33) and, in turn, is stimulated by the duodenal secretin (32). Its work is also enhanced by the spleen (34).

The Psychic Control of Endocrinous Action.—The production of the secretions of the ductless glands is not under the control of the will, but the mind evidently has an influence upon certain phases of endosecretory activity. Such psychic states as fear, rage, or pain, have been definitely proved to stimulate the production of adrenaline. Cannon's experiments, which prove this, are referred to more fully in Chapter XVIII.

A New Idea in Organotherapeutic Preparations.—Münzer[19], in commenting on the well-established fact that the ductless glands seem to work in pairs, one of each pair stimulating and the other checking certain functions, has made a suggestion well worth considering. Since, by the operative removal of the gland that does the checking, the stimulating gland is left in full control, and the function of which it has charge receives only the stimulating activation, one arrives at the logical conclusion that, before utilizing glands for organotherapeutic purposes, their antagonists should be removed. Münzer cites as an example Cushing's recent research on carbohydrate tolerance before and after removal or exclusion of the posterior lobe of the hypophysis. His experiments all demonstrate that the posterior lobe has an inhibiting

action on the oxidation of carbohydrates, and is thus an antagonist to the pancreas, which, as we know, is concerned in the oxidation of carbohydrates. For organotherapy, therefore, a pancreas should be used which has been previously activated by removal of its antagonist, the infundibulum. This writer goes so far as to state that only in this way will organotherapy accomplish what has been hoped from it, and its use be extended.

This is a difficult suggestion to carry out, not merely from financial considerations, but because of the complexity of the relations of the hormone-producing organs. The example referred to proves this, for we have already seen that pancreas antagonism is not confined to the pituitary, but that the thyroid and adrenals also have a similar restraining action.

The Loss of the Hormone Balance.—It will be seen that there is abundant opportunity for the blood-plasma to become deficient in respect of its hormonic constituents. The hormone balance may be very easily disturbed. There may be too much, too little, or a perversion of any single hormone, and these defects may be combined in numerous ways, causing many disturbances, each of which has its own peculiar effect upon metabolism. From the above, it is evident that the intricacies of the hormone balance are fully as complicated as those of the nervous system, and it does not seem to be an overstatement to say that they are fully as important. The importance, then, of a knowledge of the antagonisms and synergisms of the various hormones must be clear. With a knowledge of these facts, it is possible to give a physiologic reason for many organotherapeutic procedures.

The loss of the hormonic balance is written large in the morbid phenomena of the human body, and its restoration forms a main principle of modern therapy. The part

played by the hormones in the destruction of toxins is another important function. There is undoubtedly a great future before hormone therapy, and a knowledge of its present application is essential to all who practise the art of medicine.[20]

The Modification of Disorders of the Hormone Balance.—Two statements may well be added as a final touch to this chapter. One by Ott[21] reads thus: "In deficiency or loss of internal secretions we substitute by giving the gland by the mouth. In excessive internal secretion of the gland we can overcome it by its antagonistic gland." The other, by Blair Bell,[22] is as follows: "No experimental finding in regard to the interrelationship of the internal secretions can be regarded as of real or practical value unless it be supported by clinical evidence." Hence it is for the practical clinician to apply himself to the task of establishing or refuting the large and ever-increasing number of suggestions made by the experimentalists. Much of the clinical experimentation, no doubt, will be contradictory and unsatisfactory, but much will be of the most encouraging nature; for, as an editorial writer in the *Medical Press and Circular*[23] says: "In some cases [referring to those treated by pluriglandular therapy] it must be admitted that the results obtained seem to be little short of miraculous"; and we must persist in our attempts regardless of failure, for, as this same writer continues: "On the other hand, the many failures point to the fact that there is a great deal yet to be understood and many difficulties to be overcome before hormone therapy can be said to rest on an absolutely scientific basis."

All of which goes to show the vital importance of a knowledge of the hormone balance, as well as to lay the foundation for a method of treatment which will, it is

confidently believed, eventually revolutionize medical practice. In the sections which follow, an attempt has been made to bring into review a part of what has been done in this direction, in order that the ways in which an aggressive study of hormone action and therapy the more conveniently may be made clear.

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CHAPTER IV

DO THE SALIVARY GLANDS PRODUCE A HORMONE?

Salivary Digestion in the Stomach—Certain Heat-Stable Active Principles—The Saliva activates Pancreatic Digestion—The Relation of the Salivary Glands to other Endocrinous Organs—The Relation of the Parotids to the Gonads—Parotid Therapy in Ovarian Disorders.

THE function of the salivary glands is generally considered to be limited to the production of saliva, a slightly alkaline watery fluid whose principal function is to facilitate mastication and deglutition by moistening the food.

A secondary, or perhaps equally important, function is that of producing a starch-splitting ferment—ptyalin—which, however, has not so much opportunity to accomplish its task as it should have, because of the usually brief contact with food in the mouth or its neutralization by the gastric acid; for ptyalin is active only in an alkaline medium.

Salivary Digestion in the Stomach.—According to Starling,[1] however, the food mass, on reaching the stomach, is penetrated only with difficulty by the acid gastric juice, which is secreted by the mucous membrane of the stomach within five minutes of the taking of the food. Even half an hour after a meal the interior of the mass of food in the stomach may be still found to be neutral or slightly alkaline. The food, therefore, thoroughly moistened by and mixed with saliva, remains in the stomach for thirty to forty minutes before the salivary ferment is destroyed

by the penetration of the acid gastric juice. During this time the ptyalin continues to exert its effect, so that we may say that the chief part of the salivary digestion occurs actually in the stomach, and may result in the almost complete alteration of the starch into dextrin and maltose

Certain Heat-Stable Active Principles.—Several investigators have shown that the activity of the saliva is evidently not limited to its contained ptyalin. It is well known that this ferment is destroyed by heat, yet Roger[2] has shown that saliva submitted to a heat of 85° to 100° C. for some time, is not completely inactive, for when mixed with fresh saliva it notably augments the diastatic power. Roger's figures are interesting. He found that if one allows 0·05 c.c. of saliva to act upon 10 c.c. of a 1 per cent. starch solution for half an hour, there will be obtained 0·007 gramme of sugar; but if one adds to the mixture 2 c.c. of heated saliva, the quantity of sugar is multiplied five times, the figure recorded in exactly similar experiments being 0·031 gramme. A material reduction in the amount of heated saliva was made, and even then more than three times the amount of sugar was produced—0·025 gramme. According to this authority, one can reactivate heated saliva with a mere trace of the fresh liquid, and this seems to be a point of possible therapeutic worth.

The Saliva activates Pancreatic Digestion.—In a later communication Roger and Simon[3] have shown that the saliva has an energizing action upon the starch-splitting powers of the pancreatic juice. If the acid contents of the stomach are secured, then slightly alkalinized, and a trace of fresh saliva is added, the digestive action immediately reappears. With this in mind, an attempt was made to show that this same activating power was a factor in starch digestion in the intestine. In another series of experiments saliva was mixed with a starch

solution. Sugar-splitting immediately commenced, and then gastric juice was added and the process arrested. Upon rendering the mixture alkaline, sugar-splitting did not continue, but seemed to be definitely arrested; but on the addition of a trace of pancreatic juice—a mere fraction of a drop—the salivary activity was started again, and the amount of sugar produced was multiplied from four to five times.

Evidently, then, the saliva contains a substance which is not a ferment, but which either activates the starch-splitting powers of the pancreatic juice or is activated by it, and hence the digestive powers of the saliva are not totally lost because of its passage through the stomach. This is not a hormone, although it is not improbable that the parotid and submaxillary glands are influenced by humoral channels, just as we have learned that the majority of the other secretory glands are controlled; and while some work has been done in France with preparations of the parotid in the reactivation of starch digestion, the advantage to be gained from such medication is not likely to be so great as the simple regulation of diet and the physiologic stimulation of these glands by giving foods that require much mastication, etc. Hence salivary opotherapy as a means of stimulating the activity of the salivary glands is not generally practised.

The Relation of the Salivary Glands to other Endocrinous Organs.—A number of facts seem to indicate that the salivary glands are a part of the endocrinous system. For example, Sprinzles[4] noted that in thirty-three cases of obesity there was an enlargement of the parotid gland, and suggests that this is more than a mere coincidence. He notes that this hypertrophy is not found in persons who are merely corpulent or well nourished, but in those suffering from a type of obesity in which fat is evidently

pathologic and found mostly upon the face, breasts, and abdomen. It is inferred that this finding may be an evidence of some more or less intimate connection with the disordered metabolism responsible for the obesity.

Another endocrinous relationship of the parotid gland has been mentioned—*e.g.*, with the pancreas. Allegri,[5] in a recent communication, tells of three cases of acute parotitis ("*orrechioni*") which he believed to be the cause of a severe inflammation of the pancreas, which supervened in every case. It is entirely probable that other similar connections may have been noticed, and that the salivary glands are an integral part of the system of glands of internal secretion.

The Relation of the Parotids to the Gonads.—There is also an obvious connection between the parotid glands and the gonads, for clinical experience with mumps very frequently shows a "sympathetic" inflammation of the testicles, which must be considered as of humoral transmission. Ovarian disorder, while not nearly so common, has been occasionally seen as a sequel of acute parotitis.

Bell[6] believes that the parotids have a considerable influence upon the ovaries, but it is not likely that changes in the normal activity of the parotids cause or prevent ovarian disease. This writer, however, has used an extract of the parotid glands of sheep with what he considered good results in ovarian disorder, and reports sixty cases of enlargement and pain in the ovaries in which he was able by parotid treatment to avoid operative interference and to obtain a complete cure.

Parotid Therapy in Ovarian Disorders.—Parotid extracts have been used in the control of dysmenorrhœa with success. Mallett[7] has convinced himself that they relieve the pains with far more certainty than any uterine sedative. Other associated pelvic disorders, such as local

infiltrations, ovarian hyperæmia, and the persistent reflex headaches of ovarian origin, are considerably benefited by this treatment.

Shober[8] confirms the value of parotid extracts in the treatment of ovaritis, ovarian dysmenorrhœa, and neuralgia, and urges that the treatment be used more frequently, and continued in each case for a minimum period of two months in doses of 3 to 5 grammes of a powdered extract three times a day.

At present no further use has been found for this method of treatment, and it has "gone out of fashion," due undoubtedly to the immense progress made in the study of other organic preparations, which have been found more suitable in this class of cases.

It seems, nevertheless, that the salivary glands, and especially the parotid, are not entirely inert, either in that part of their physiological action which is related to hormone influences, or, for that matter, in organotherapy.

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CHAPTER V

THE SECRETINS AND PYLORO-DUODENAL EXTRACTS

The Discovery of Hormone Action—A Therapeutic Agent of Promise—The Specificity of Secretin Action—The Gastric Secretin—The Broader Activities of Secretin—The Establishment of the "Secretin Theory"—The Physiology of Secretin Action—Stimulating the Production of Secretin in Constipation—The Bacillus Bulgaricus and Secretin Production—The Preparation of Secretin—Secretin in Gastro-Intestinal Therapeutics—Methods of Administration—The Treatment of Digestive Insufficiencies—Possibilities in Infantile Diarrhœas—Secretin in Malnutrition and Cachexia—Experiences with Secretin in Diabetes Mellitus—The Relation of Secretin to the Hormone Balance—Dosage and Administration.

THE orthodox treatment of certain forms of indigestion has for many years included preparations of animal origin. The use of pepsin and pancreatin has been established on a firm basis, although at times dissentient voices are heard to the effect that the continued use of such preparations tends to induce laziness on the part of the organs in question, for the preparations simply serve as digestants and do not actually facilitate a regeneration of the disordered alimentary function. Our conception of the treatment of the indigestions has in the past few years been very materially modified by the discovery of certain other substances, also of animal origin, and a revolution has begun, not only in our conception of the physiology of the digestive glands, but in the treatment of their functional insufficiencies.

The Discovery of Hormone Action.—The first discovery which led up to this was when Dolinski and Gottlieb[1] noted that the introduction of dilute hydrochloric acid into the digestive canal is followed by a remarkable increase of the secretion of pancreatic juice. The researches of Popielski, Wertheimer, and Le Page established the fact that this hypersecretion was produced when the acid came into contact with the duodeno-jejunal mucosa; in other words, the contact of acid solutions with the duodenal mucosa is the physiologic excitant of pancreatic secretion.

Then came the crucial monograph of Bayliss and Starling,[2] which gave proof that this action was not simply the so-called "acid reflex" referred to by Pavlov, and that the acid did not act by itself, but by the intermediary of a hitherto unknown substance, which could be produced *in vitro* as well as *in vivo*.

This was the hormone "secretin" first isolated by these investigators in the research laboratories of University College, London, in 1902.

This proved to be one of the most important discoveries in physiological research, for it firmly established the position of the "chemical messengers," and, as we have already seen, brought into being the whole subject of hormones and their essential rôle in the functions of the body.

A Therapeutic Agent of Promise.—More than ten years have passed since the initial reports were published, and in that time scores of tests have been carried out, which have established very definitely the important part that secretin plays. For a number of years the author has been interested in the application of this idea in therapeutics, and has studied the relation of secretin and extracts of the duodenum to gastro-intestinal therapeutics.

In the matter which follows, an attempt will be made, first, to explain the mechanism of secretin action and to give sufficient proof of its powers, and then to recapitulate the fundamental facts already published, so that their relation to therapeutics may be fully evidenced; in other words, an attempt will be made here to prove that a new and revolutionary therapeutic procedure is available for the treatment of functional insufficiencies of the alimentary tract, and to further the introduction of what, because of the limited amount of literature on its use, can still consistently be called "a new method."

Hitherto the use of secretin has been mainly limited to the experimental investigators, and these, usually, have not applied it in clinical work. It is still the exception to find physicians using secretin as a therapeutic agent.

The Specificity of Secretin Action.—Secretin is a definite chemical product of the mucous membrane of the duodenum—the principal alimentary hormone. We know its chief physiological qualities, but as yet practically nothing of its chemical structure.

It has been extracted from the human duodenum after autopsy, and is found in many animals. There is no specificity of secretin for any genus—that is to say that it is presumably identical, irrespective of its source—hence, secretin procured from animals is active in man, and *vice versa*. According to Sweet and Pemberton[3] the activity of secretin-bearing preparations for laboratory testing varies greatly. The extracts generally used in experimental work are made from the dog. They found that sheep extract is the most active of any that they have used, and also state that the human intestine is not only relatively, but actually lower in its content of prosecretin than is the intestine of some lower animals. This is in

harmony with the fact that the digestive activities in man are not so great as in other animals—*e.g.*, as the dog or pig.

The Discovery of Secretin.—The story of the discovery of secretin may be briefly recalled. In the investigation of the properties of enterokinase, that remarkable tryptic activator first discovered by Chepovalnikov[4] in Pavlov's laboratories at St. Petersburg, Bayliss and Starling noted the phenomenon already mentioned—viz., that the injection of acid or acid chyme into a loop of small intestine was followed by a secretion of pancreatic juice. They further found that this occurred even when all nerve channels had been destroyed. These investigators were convinced that the message from the intestine to the pancreas was carried not by the nervous system, but by the blood; they concluded, therefore, that the activating substance was produced in the duodenal walls under the influence of the acid, and that it was then absorbed into the blood and served to excite pancreatic function. A portion of the intestinal mucous membrane was accordingly scraped, pounded up with dilute hydrochloric acid, and filtered. Injection of a portion of the neutralized filtrate into the blood of an animal resulted in a copious flow of pancreatic juice, and the chemical messenger, or hormone, responsible for this action was named "secretin." Later it was called "pancreatic secretin," to distinguish it from other similar substances which excited other glands.*

The Gastric Secretin.—Since this epoch-making announcement was made, other investigators, notably Edkins,[5] have shown that the gastric walls near the pylorus produce a similar hormone, which has been called "gas-

* Further interesting references to this whole subject will be found in Starling's "Principles of Human Physiology," 1912, p. 797.

trin " or " gastric secretin." For all we know there may be no essential difference between the gastric and duodenal secretins, save only in the cells which they activate. Its action is through the blood and upon the peptic and oxyntic glands of the stomach.

In a recent editorial reference[6] to the gastric secretin the results of this work are concisely outlined as follows: " Edkins has carried out experiments to see whether such a chemical mechanism, in distinction from the nervous control which is usually called on to elucidate the phenomena of secretion, may not also serve to explain the secretion of the gastric juice when food is introduced into the stomach. He finds that substances such as peptones, broths, dextrin, etc., which are known to induce gastric secretion when ingested, are without influence on the secretory act if they are injected directly into the blood-stream; but when such known excitants of secretion are allowed to stay with the pyloric mucous membrane, and a decoction of this is then injected into the circulation, a secretion of both acid and peptic enzyme into the stomach ensues. Infusions of the cardiac portion of the stomach or of other organs do not act in this secretion-producing manner. Edkins concludes that this typical secretion of gastric juice is determined by a chemical mechanism. The first products of digestion act on the pyloric mucous membrane, in which they produce a substance which, entering the blood-stream, is carried to the gland-cells of the stomach, where it acts as a specific excitant of their secretory activity; this is the gastric hormone—'gastric secretin.'"

As will shortly be shown, just as secretin is not completely formed in the duodenal cells, but is changed from its precursor prosecretin into secretin by contact with an acid, so the gastric secretin—gastrin—remains in the

orm of a precursor—progastrin—until either the products of digestion or the psychic stimulus of food changes this inert substance into the chemical activator—gastrin—which is not secreted into the stomach, but which, by humoral channels, is brought back to the secreting cells of the stomach. The following diagram may make this clear. (Fig. 5.)

Prosecretin and Secretin.—Secretin is evidently not preformed in the duodenal walls and stored up there in quantities ready for use; it is made as needed, and the precursor of secretin, or "prosecretin," as it has been called, was thought by Bayliss and Starling to be changed by the acid contact into the active hormone. This has

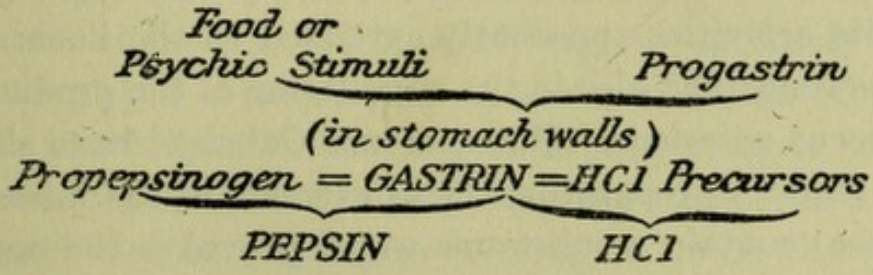


FIG. 5.—THE FACTORS CONCERNED IN PEPSIN PRODUCTION.

been the subject of considerable controversy, and Delezenne and Pozerski[7] seem to have proved that secretin may be extracted from the duodenum without recourse to acids, and state that it is simply liberated by the acid contact. These writers bring indisputable evidence to show that secretin pre-exists in a definite form in the mucosa, and that there is a hindering substance which prevents its liberation. This substance is rendered inert by the acid (and by other means), and the secretin is permitted to be passed into the blood. They relate numerous methods of extracting it, and state that, irrespective of the method of extraction, the product—secretin—is always the same.

Whether or not this is correct is too technical a question to interest us. It suffices that it passes into the blood when intestinal digestion is about to begin, and excites the three organs concerned—the pancreas, liver, and intestine—as we shall now see.

The Broader Activities of Secretin.—Some of the French physiologists have proved that secretin not only influences the gastric and pancreatic glands, but also stimulates the production in the duodenal walls of the same substance. Shortly after Starling's announcement, Delezenne and Frouin,[8] working at the Institut Pasteur in Paris, confirmed his statements and demonstrated that the action of secretin was broader than had been supposed; for it did not exert itself solely on the pancreas, but its activities apparently extended to the ileum, and it was concerned also in the stimulation of the production of succus entericus. Bottazzi and Gabrieli[9] have shown that secretin preparations (acid extracts of the intestinal mucosa) contain a substance which provokes the normal flow of intestinal juice; it has clearly been shown by a number of experimenters that secretin also stimulates the functional activity of the liver. Clinically, too, it is evident that secretin preparations do not influence the stomach and pancreas alone, for it will be frequently noted that acholic clay-coloured stools resume their normal colour following a few doses of this remedy. Hallion[10] notes that secretin has also a distinct influence upon the liver and the motor functions of the bowel. In his experiments, in which he was associated with Enriquez,[11] he noted that secretin also increases in a great measure the secretion of bile. These writers observed that almost invariably during experiments on animals injections of secretin were shortly followed by evacuation of the bowels. This fact has been put to good use in the

treatment of certain forms of constipation, and is fully considered in Brégeon's thesis, and has been carefully confirmed by Portier, Falloise,[12] and others.

The Establishment of the "Secretin Theory."—The St. Petersburg School has long opposed the "secretin theory." Bylina,[13] as late as in 1911, intimated that secretin was not quite what Bayliss and Starling had made out, stating that the pancreas possesses a constant secreting function for which nervous influences are principally responsible. In a later paper[14] he admits that the pancreatic secretion to a certain extent is dependent upon a humoral mechanism; but he still asserts that nervous influences are concerned in the excitation of pancreatic secretion, and, indeed, determine the chemical character of the juice. Popielski[15] insisted similarly that secretin played a minor part in the stimulation of pancreatic secretion, and that the results purporting to be due to its influence were obtainable in other ways. In Italy, Luciani[16] and his colleagues have agreed with this position, and bring forward experiments which are supposed to prove the fallacy of Starling's position.

Experiments seem to discount these statements, however, and the most conclusive proof of the error of Bylina's idea is to be found in a 100-page thesis,[17] which gives the details and deductions of Hustin's interesting studies of the mechanism of the external secretion of the pancreas, carried out at the Institut Parc Leopold, in Brussels. The subject is very thoroughly discussed, the importance of secretin being emphasized in a most convincing manner, and certain of the experiments being apparently decisive. Among other things Hustin has demonstrated that the pancreatic secretion cannot be stimulated by secretin alone; he has proved that a certain element in the blood must be associated with the secretin. His

method consisted in taking the pancreas from an animal, placing it in a bath of liquid paraffin, overlaying water at 38°C., and then irrigating it with liquids, which were introduced by means of a cannula through the pancreatico-duodenal artery, and were conveyed away by another cannula in the portal vein. A third cannula was introduced into the duct of Wirsung, to lead off the pancreatic juice. As a result of numerous experiments Hustin established the important fact that a gland irrigated independently with Locke's physiological serum, blood, or secretin solution gives no secretion, but irrigation with a mixture of blood and secretin gives an abundant secretion of clear liquid containing trypsinogen, lipase, and amylase—results that can hardly be gainsaid. The author further states that secretin is used up in the gland in the impregnation of the pancreatic cell, in a manner that renders it sensible to the action of certain substances in the blood. The presence of calcium electrolytes is stated to be a third essential (see diagram on p. 64). For convenience Hustin compares this action with the side-chain theory of Ehrlich—viz., that living protoplasm carries certain chemoreceptors or contains chemoreceptive substances, and it is by combination with these that drugs, etc., induce their specific effects.

Recent reports from St. Petersburg seem to indicate that at last there is a tendency to admit that the "secretin theory," so long discounted by certain Russian and Italian physiologists, is no longer so untenable. Sawitch and Zeliony,[18] reporting a series of experiments which were carried out in the physiological laboratory of the Military Medical Academy in St. Petersburg, have established the essential accuracy of Edkins's contention that normal gastric secretion is due to the co-operation of at least two factors—the one a nervous element induced by

the stimulation of the mucosa of the mouth or by the awakening of the appetite through psychic channels, and the other a chemical factor dependent on the elaboration of a hormone which acts as a chemical messenger to all parts of the stomach through humoral paths, and whose effects linger long after the psychic stimulus has disappeared.

In his book on "The Action of Medicines,"* Brunton illustrates his statements by means of a diagram (Fig. 6). This diagram (for permission to use which I have cordially

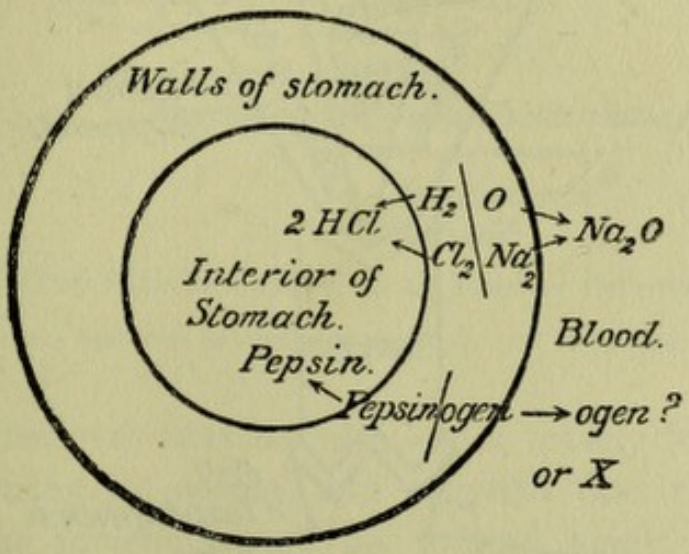


FIG. 6.—DIAGRAM TO ILLUSTRATE THE CHEMICAL CHANGES DURING GASTRIC SECRETION.

to thank this distinguished therapeutist) shows that it was hardly possible, before the discovery of the hormones, to explain the phenomena of gastric digestion without presupposing the presence of an indefinite entity. It is evident that in this diagram, which is intended to illustrate the chemical changes during secretion, the unknown quantity, or *X*, is no other than secretin, or, rather, in this particular case, gastrin, or gastric secretin.

A very similar, and perhaps identical, hormone is probably produced by the spleen, the function of which

* Edition of 1897, p. 50.

is to stimulate the digestive glands to do their normal work. This splenic hormone has been proved by numerous physiologists to have a part in the activation of trypsinogen.

The Physiology of Secretin Action.—Dixon and Hamill[19] made a series of experiments at the pharmacological laboratory of Cambridge University, to test the hypothesis of Ehrlich (which has been referred to above). This is also illustrated by Hustin's deductions, which are

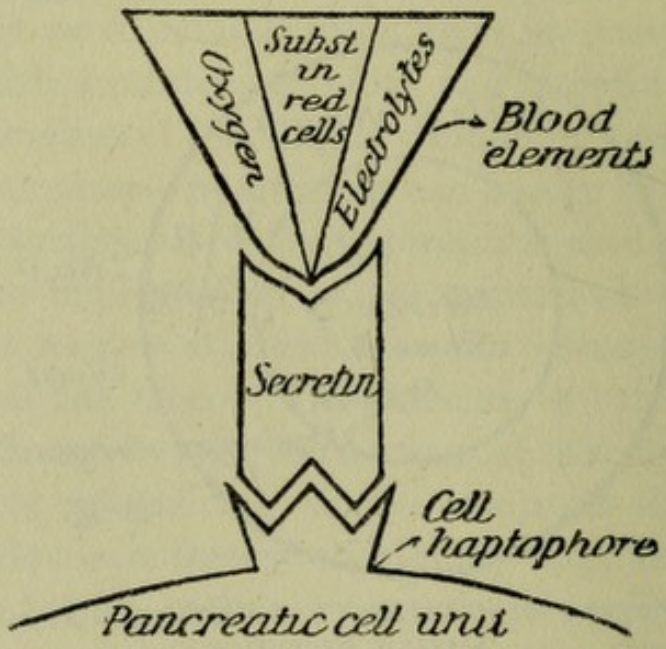


FIG. 7.—SCHEMATIC REPRESENTATION OF SECRETIN ACTION (BASED ON EHRLICH'S HYPOTHESIS).

explained in Fig. 7, which is a modification of that of Hustin. Secretin was investigated first, as its marked action on the pancreas was already known. As a result of this work, the physiology of secretin action is now better understood. The prosecretin 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 enterokinase in the intestinal canal. The action of secretin, then, may be conveniently expressed by the following equation:

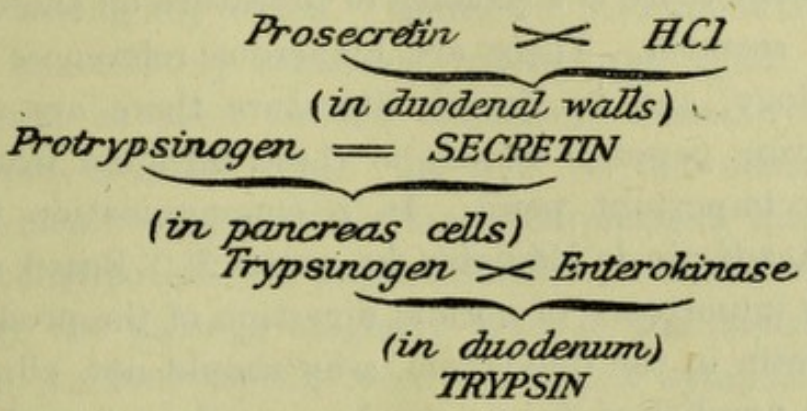


FIG. 8.—THE FACTORS CONCERNED IN TRYPSIN PRODUCTION.

(*Note.—The* = *indicates by humoral channels, and* x *by direct contact.*)

Hallion believes that secretin is not totally lost or destroyed during its action, and suggests that the whole part of the molecule may be utilized again, as some authorities are now beginning to suppose is the case with the ferments. Hallion, at least, reports that subcutaneous injections of secretin, which had no secretory influence, were not without some effect, for the duodenal mucosa of the animals thus treated showed considerable redness and a special richness in secretin precursors, producing, when influenced by acids, an abundant internal secretion of secretin.[20] This is in harmony with the statement of this same investigator regarding the specific action of the

* Professor Starling, in an annotation upon the manuscript of this chapter, writes: "I could not confirm these experiments, nor could Mellanby. I do not believe they are correct." There can be no doubt, however, of the stimulating action of secretin, the rather indefinite point being just how this is brought about.

hormones upon the internal secretory capacity of the corresponding hormone-producing tissues, and also with a statement attributed to Starling: "Secretin not only causes the outpouring of the digestive secretion, but at the same time brings about the formation of new enzyme material."

Stimulating the Production of Secretin in Constipation.—At present there is a paucity of literature on the clinical use of secretin. There are numerous references to its physiology, and in French literature there are several interesting papers. In one of these Enriquez brings up a very important point. In a communication to the Paris Académie de Médicine he writes:[21] "Based on the greater importance of normal digestion of the production of secretin in the duodenum, why should not, clinically, a large number of dyspepsias be secondary to a disturbance in the highly specialized function of the duodenal mucosa?" "When it is remembered," he continues, "that secretin also possesses an incontestable influence upon intestinal motility, one of the first and most constant signs of secretin insufficiency must, without doubt, be clinically represented by constipation. Thus, guided by our experimental research, we have found a means of stimulating this function in certain constipated dyspeptics." Enriquez prepared keratin-coated capsules of gluten, containing an active and harmless acid (tartaric), which was proved experimentally to be stable in the stomach and easily destroyed in the duodenum.

The results of this form of medication were most interesting. All the patients showed a more or less noticeable constipation, and in seven of the cases it was the dominating symptom, inconveniencing the patients as much by its persistence as by its obstinacy. In these seven cases acid medication of the duodenum brought about, with

varying ease according to the dose, a stimulation of the secretory and motor functions of the intestine and a regulation of the stools. Two cases were of special interest. One was that of a person suffering from localized sclerosis (*sclérose en plaques*) for many years, with intractable constipated periods lasting from six to eight days and resisting many kinds of purgatives, enemas alone having any action. Under this treatment the stools were immediately regulated, giving way again to constipation as soon as the treatment ceased, and this occurred several times. In five of the observations muco-membranous colitis was complicated alternately with constipation and painful abdominal crises, terminating by the passage of glairy mucous and membranous casts. In four of the cases the colitic symptoms were much relieved at the same time as the constipation.

It will be noted that Enriquez did not administer a preparation of secretin; but, of course, the principal value of this method depends upon the production of secretin, which is artificially stimulated by replacing the evidently missing HCl with another equally efficacious acid. There may be cases in which the duodenal cells will not be stimulated, and here it would seem that secretin itself could be used to good advantage.

The author has personally noticed, and his experience has been confirmed by several correspondents, that the administration of preparations of secretin is followed quite constantly by the relief of fermentation in the upper bowel, and the reason for this is not far to seek. Gastric and intestinal fermentations are mainly due to a deficiency in the amount and activity of the digestive juices, as it has long been known that the administration of hydrochloric acid not only favours the digestive action in the stomach, but also tends to increase the amount of

pancreatic ferments in the duodenum, and only since the discovery of secretin has it been clear how this is brought about.

The Bacillus Bulgaricus and Secretin Production.—An interesting fact has been established by Beveridge of New York regarding a possible relation between sour-milk therapy and the production of secretin. It is well known that normal secretin production is caused by a stimulus to the duodenal mucosa by an acid—usually the acid chyme passing from the stomach. Beveridge has secured some excellent results in the treatment of diabetes with cultures of the *B. bulgaricus*, and in his article[22] he writes:

"The power exerted through the stimulation of acid digestion in producing secretin, so necessary to the normal functioning of the pancreas, has never, until now, been brought forward as a factor in glycosuria; hence, one can readily perceive that when chronic conditions arise to change the acidity of the gastric contents, a corresponding response will be noted in the production of secretin. According as an increased acidity or lowered acidity of the gastric chyme is apparent while passing through the duodenum and upper portion of the small intestine, the amount of secretin manufactured is either increased or diminished, and, reflexly, the pancreatic secretions will also be increased or diminished. Should this abnormal chemical reaction continue, whereby the pancreas receives inadequate stimulation during digestion, serious chemical and metabolic changes will in time manifest themselves, which may eventually combine and prevent complete carbohydrate metabolism.

"The other causes interfering with a normal production of secretin are intestinal putrefaction, ulcer of the duodenum or pylorus, and any lesion involving the mucosa

of the duodenum and upper portion of the small intestine."

The value of Beveridge's treatment, then, does not lie only in the favourable influence of the *B. bulgaricus* upon intestinal putrefaction, but is due also to the acid stimulus to secretin production caused by the lactic acid, which is a normal product of these micro-organisms. This subject is deserving of much wider study and application.

The Preparation of Secretin.—Secretin is not particularly difficult to obtain. As already mentioned, Starling secured it by pounding up duodenal scrapings with hydrochloric acid. Various methods of extracting secretin are outlined in articles by Bayliss and Starling,[23] Stepp,[24] Gley,[25] and Launoy.[26] Aqueous solutions of secretin are easily made, but they must be used while fresh, for, if left unstoppered, they lose their activity in about twenty-four hours. If, however, they are preserved in sterile ampoules and kept in the dark, they remain active for some time. Sweet and Pemberton[3] have found that sterile preparations keep for as long as nine weeks, but gradually lose their excito-secretory powers.

Fortunately, dried extracts of duodenal mucous membrane keep well, and from them potent solutions are now made in America, France, and England. Provided that in this manner one can stimulate the production of hydrochloric acid in the stomach, the rest is simple. The passage of the acid gastric contents into the intestine will be a natural stimulus to the production of secretin, so that the administration of such a remedy serves a double purpose; it will stimulate the pancreas directly, and also indirectly, by the production of an additional supply of this important activator.

Secretin in Gastro-Intestinal Therapeutics.—From the foregoing experimental facts it will be seen that in this

remarkable substance, or series of substances, we should have a therapeutic weapon with vast possibilities. This is especially true when we remember Starling's[27] own statement: "It is now a demonstrated fact that a large share of the wonderful co-ordination of the activities of different parts of the body, which determine their mutual co-operation for the common weal of the organism, is played by the production and circulation of chemical substances which are strictly analogous to the drugs employed during countless ages by mankind in the treatment of his diseases." It does not seem that the analogy is as thorough as the foregoing quotation would indicate, for the use of secretin and other hormones is infinitely more reasonable, and its stimulating effect far more nearly physiological, than that of other means to the same ends.

Before proceeding to the consideration of the clinical possibilities of secretin preparations, a few facts concerning the stability of secretin as a remedy and its administration deserve to be referred to.

Methods of Administration.—In practically all animal experiments with secretin, this substance has been administered by the intravenous method, and it has been stated more than once that secretin given by other methods —*e.g.*, when taken into the stomach—is not active (Starling).[28] We have already seen that Hallion found that hypodermic injections had a marked influence upon the duodenum, although they did not give a secretory response comparable to the intravenous injections.

Some experiments have been made, the results of which indicate that in animals secretin is not absorbed when introduced, even in large doses, into the digestive canal; but clinical tests, covering a period of several years, have proved that neither the conditions in the stomach during digestion nor those in the intestine, prevent secretin from

entering intact into the circulation, and while the rapidity is not so great, otherwise it is just as it is given direct in the experimental work. It is therefore available as a chemical excitant of the various cell units which respond to its activation.

Of considerable importance in this connection is the fact that Camus and Gley[29] have secured secretin from the mucosa of the stomach (thus amplifying Edkin's work on gastrin), and have shown that secretin in neutral solutions is slightly weakened by the alkaline pancreatic secretions, but that it remains the same in acid solutions. It is only necessary, then, to give a preparation of secretin containing sufficient acid, when its properties are preserved. It has been supposed that the alkalinity of the intestinal juice would destroy the secretory powers of this hormone, but the work of Delezenne and Pozerski has shown that this fear is unfounded. If, in effect, the intestinal extract in solution destroys secretin, this destructive action does not manifest itself with acid extracts; thus, in order to paralyze the opposing substance, or antisecretin, which destroys its action, it is necessary only to insure an acid medium.

Undoubtedly a comparison between the results of the intravenous injection of secretin solutions and the oral administration of solid or liquid extracts of the duodenal mucosa would give evidence in favour of the direct method —intravenous medication for obvious reasons is more rapid, active, and pronounced than any other method of giving drugs—but any statements to the contrary notwithstanding, one cannot overlook the noticeable influence on digestion and nutrition which follows the administration of secretin by mouth; this will be still more apparent when all the evidence is considered. It must also be remembered that, in the preparation of secretin,

boiling with dilute HCl is a part of the process, and any conditions compared with this which might be found in the stomach would seem theoretically to be negligible; in fact, in practice the oral administration of secretin accomplishes definite results which are sometimes nothing short of marvellous.

The Treatment of Digestive Insufficiencies.—Very little clinical work seems to have been done with secretin in the English-speaking countries. The only articles referring to secretin-containing preparations that have been found in a very careful search of English and American medical literature are those on its possible use in diabetes (*q.v.*), those by the present author,[30] and one from the pen of Boardman Reed.[31] In this article he compares his standard pepsin-hydrochloric mixtures, referred to in his excellent book,* with an elixir containing gastric and pancreatic secretins, and finds that these organic principles are considerably more active, rapidly bringing the work of the stomach to the normal, and usually at the same time improving the intestinal indigestion and assimilation. Reed states that "secretogen is apparently the most powerful excitant of gastro-intestinal secretion so far tried by me," and refers to a number of cases, one of which is mentioned in an addendum to his paper, which follows: "Since the foregoing was written, I have examined chemically the stomach contents of one of the patients referred to, in which none of the secretogen has been taken for a month, and the proportions of both the free and combined hydrochloric acid were found still a little above normal, though, before the remedy was taken, there had been no free hydrochloric acid at all, and the proportions of both the combined hydrochloric acid and of the total acidity had been decidedly below normal."

* "Diseases of the Stomach and Intestines," third edition, New York, 1911.

Possibilities in Infantile Diarrhœas.—Personal experiences fully confirm Reed's statements, and attention has been called by Harrower[32] to the encouraging possibilities of this preparation in the treatment of the gastro-intestinal disorders of small children, especially those prevalent in the summer. Two paragraphs from this paper will give the gist of the idea: "Since secretin exerts a very effective stimulus to the gastro-intestinal function, this stimulation is normal and physiologic, and usually followed by no reaction. Flatulence and fermentation seem to be controlled very effectively, and limited experience with infantile indigestions, and especially the summer types, shows that this is a means of treatment worthy of further study and consideration.

"It cannot be denied that by far the best antiseptics for the reduction of toxic conditions in the intestine are its natural juices. Secretin plays the most important part in their production, and its influence is not limited to the stomach or pancreas; but including these important organs, it also influences the production of bile and the intestinal juices from the pylorus to the ileum. The augmentation of the amount and activity of the normal digestive secretions is the most reasonable means of checking the intestinal fermentations so common in children, and it is well to remember that the administration of secretin does not in the least interfere with the hydrotherapeutic and even the present-day drug treatment of these conditions."

It may seem paradoxical to suggest the same remedy for constipation and diarrhœa, but the facts show that secretin-bearing preparations are valuable for both.

Secretin in Malnutrition and Cachexia.—It is well known that there is practically always a complete ab-

sence of hydrochloric acid production in cancer and gastric cancer, and the lack of hydrochloric acid—the physiological stimulus to normal secretin production in the duodenal walls—results in a marked decrease in the amount and efficacy of the pancreatic ferments, as well as of the whole digestive cycle. This nearly suffices to account for the nutritional disorders which are pathognomonic of carcinoma. With the foregoing in mind, it can be readily appreciated that secretin may be used in cancer and cachexias generally, not to influence the disease *per se*, but rather as a means of increasing the digestive activities and nutrition; the same ideas naturally hold good in other conditions, where toxæmias, superfunction, or asthenia, have lessened the digestive capacity. In no disease is this influence more desirable than in tuberculosis, and attention is already being turned to the possibilities of this new adjunct remedy for the digestive disorders of the tuberculous.[33]

Secretin in Diabetes Mellitus.—Since the numerous confirmatory reports of the action of secretin on the external secretion of the pancreas, as well as upon the intimate relation between pancreatic activity and carbohydrate metabolism, secretin has been recommended as a means of treating diabetes.[34] Much was expected from its use, because several very good results occasionally followed its early administration in this disease. There seemed to be good reasons to anticipate success, for the basis of this application of secretin therapy was the clear physiological evidence of a connection between pancreatic activity and diabetes, as well as between secretin and pancreatic activity; and where functional disorder of the pancreas was present, it was presumed that advantage might follow the stimulus caused by the secretin.

In their first communication on this subject, Moore

Edie, and Abram[35] described three cases of diabetes in which improvement followed the oral administration of an acid extract of duodenal mucosa. As a result of this treatment, the sugar diminished gradually, and finally disappeared. Later these same authors,[36] whose work in the meantime had been augmented by the discovery by Bainbridge and Beddard,[37] that in many diabetics prosecretin is absent from the duodenum,* admit that the majority of cases treated in this manner showed no appreciable change in the sugar output. They call attention, however, to the fact that "in some of these negative cases there has been noticed an improvement in the digestion, and in certain cases the patient's weight has increased." In one case in particular this incidental influence on digestion was very decided. "Almost at once the dyspepsia from which he was suffering was relieved, and his general nutrition improved to such an extent that he regained over 18 pounds in weight, and this improvement was accompanied by a complete recovery of his mental and physical energies."[36] Crofton[39] of Dublin also recommends secretin as useful in diabetes, and Beveridge,[22] in his experiences with the *Bacillus bulgaricus* treatment of this disease, infers that deficient secretin action is concerned in the disorders of metabolism that characterize diabetes mellitus.

Unfortunately there have been too many failures to stimulate a really extensive series of clinical tests. It

* It is interesting to note that Evans[38] made a series of experiments at the Institute of Physiology, University College, London, to ascertain the fate of prosecretin in depancreatized dogs. The information thus gained shows that total extirpation of the pancreas is rapidly followed by complete disappearance of the precursor of secretin in the duodenal walls; but if a small portion of the pancreas is left (to preserve a sufficient amount of the pancreatic hormone for the prevention of glycosuria) there is no appreciable diminution in prosecretin. It is suggested that the loss of secretin in pancreatic diabetes is simply one symptom in the general train of metabolic disturbances consequent on loss of the internal secretion of the pancreas.

seems, however, that the failures that have been reported are due, not to lack of activity in the secretin preparation or to its administration, but rather to the fact that the external secretion of the pancreas plays a very minor part in the carbohydrate metabolism. The internal secretion, on the other hand, has a specific influence on sugar combustion, due, in all probability, to the so-called "Langerhansian hormone," which is now known to antagonize the chromaffin hormone produced by the adrenal system (see Chapter VII.), and that the influence of secretin on the production of the pancreatic internal secretion is almost negligible, or, at least, decidedly less than upon the digestive, or external, secretion.

There seems to be a good field for clinical research in the application of a combination of the duodenal and pancreatic internal secretions in the treatment of diabetes, for this disease at first is essentially a form of indigestion, or, at least, very commonly associated with digestive disturbances, and, as we have seen, secretin does favour the digestive processes of the upper bowel.

The Relation of Secretin to the Hormone Balance.—If the duodenum is a part of the endocrinous system, and everything points to the correctness of this assumption, it would seem that in some way it should be related to other endocrinous organs; this is undoubtedly the case.

With the essential antagonism of the pancreas to certain other glands (adrenals, pituitary, etc.) in mind, we may at least look in this direction for evidence of a similar antagonism to secretin. Some experimental evidence to prove an antagonism by the adrenals and pituitary has been brought forward by Sweet and Pemberton,[40] who show that the removal of the adrenals induces a flow of pancreatic juice which "has been equalled in duration and activity only by the processes which depend on

activation by duodenal secretin." These same investigators previously[41] showed that "the suprarenal glands and the nervous moiety of the pituitary body in dogs contain something which, on extraction with salt solution and intravenous injection into dogs, cuts short the flow of pancreatic juice, after the administration of secretin; it also prevents the stimulation of the gland by secretin if its injection precedes the secretin."

This may be a part of the reason why secretin has been of some value in diabetes, since it is well known that both the chromaffin and posterior pituitary hormones favour glycosuria and occasionally may cause glycosuria.

Dosage and Administration.—It has been shown that secretin cannot be obtained in a pure state, at least, for pharmaceutical purposes; but that very active secretin-bearing extracts can be made from the duodenum and pylorus.

We have also learned that, since the hormones act in very minute quantities, and an important part of their action is to cause an increased product of the corresponding hormone in the body, small doses are very efficacious. It must also be remembered that hormones are activators, and many experiments have proved that a trace of a hormone (see the experiences with saliva in Chapter IV.) causes a very marked result, and they cannot be compared with, let us say, strychnine or the hypophosphites; hence large dosage is not necessary.

From 1 to 3 grains of secretin-bearing extract is a sufficient and active dose, and it may be repeated every fifteen to twenty minutes for an hour or even two, and the dosage will regulate itself after a few days. It should be added that this medication is most effective when continued in small (but sufficient) dosage for several weeks or even longer.

It is not harmful, although there are certain contra-indications, chief among which is functional hyperactivity, such as hyperchlorhydria, gastric and duodenal ulcer, etc. Reed[31] gives a word of caution regarding large doses: "I take issue decidedly with those who advise much larger doses on the theory that we should approximate the dose as nearly as practicable to the quantity which Nature secretes normally. I am sure that the large doses often fail when smaller ones would succeed, and explain this observed fact by the principle frequently insisted upon by me, that all active drugs are capable of exerting two opposite effects, according to the size of the dose. . . . It should be added, and strongly emphasized, that we should never prescribe an active stimulant of any of the digestive glands, or permit in the diet any condiment having a like effect, without a knowledge of what glands are at fault. . . ."

Readers who are interested in the study of the pancreatic secretion are referred to a valuable 132-page monograph by Terroine,[42] which considers every phase of the subject. The bibliography is very complete, especially as regards secretin.

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CHAPTER VI

OTHER EXTRACTS OF ALIMENTARY ORIGIN

Extracts of the Gastric Mucosa—The Activities of Extracts of the Intestine—A Motor Excitant in Intestinal Extract—The Depressor Action of Intestinal Extract—A Remarkable Uterine Stimulant—The Detoxicating Power of Intestinal Extract—The Hormone Influence of the Appendix.

As we have seen, a very important hormone is elaborated in the duodenal walls, and is obtainable for therapeutic purposes in extracts of this part of the intestine. In the previous chapter reference was also made to the hormone activity of extracts of the pyloric end of the stomach. Here it is proposed briefly to consider the therapeutic possibilities of other extracts of the stomach, certain parts of the intestine, and the vermiform appendix.

The chief characteristic of a hormone consists in correlating the activities of the body, the product of one organ inducing activity of another more or less remote from it. It has been noted by Aarons[1] that "it is an essential peculiarity of most hormones that they act on other organs of the body, whereas the hormones of the gastro-intestinal tract have no influence on the general system. The hormones of the digestive apparatus act on the digestive secretion."

It will be clear, then, that the principal usefulness of hormone-bearing extracts of the various parts of the digestive tract will be confined to their influence upon

the digestive activities; and their capacity in this direction deserves to be studied more extensively and applied more frequently in clinical therapeutics.

Extracts of the Gastric Mucosa.—There is no doubt that preparations of the gastric mucosa have a therapeutic influence, probably due to their hormone content. It is not unlikely that the gastric secretin discovered by Edkins, or other similar substances, are produced in parts of the stomach other than the pylorus, and hence extracts of the stomach might be supposed to have a therapeutic influence in stimulating this organ to greater physiologic activity. Gilbert[2] has stated that the powdered extract of the gastric mucosa possesses a more active and comprehensive influence than pepsin, and has the advantage of being much easier to obtain; it is also considerably more convenient and stable than natural gastric juice obtained through the fistula. Its action, of course, is different from that of pepsin in that it manifests only a limited degree of digestive activity; but it is none the less valuable, because it serves to stimulate the lagging cells to more satisfactory service.

It will shortly be seen that Zuelzer and his collaborators procured an extract of stomach walls which, when given intravenously, caused a considerable increase in peristalsis, and it is quite possible that preparations of this character might be used to advantage in the treatment of constipation.

According to Byla,[3] a preparation called *exo-gastrine*, which is a substitute for natural animal gastric juice, as well as for the commonly used pepsin-HCl mixture, is used in France. It is obtained by extraction by exolysis of the macerated scrapings of the stomach walls of pigs in the presence of glycerine. This is said to be an excellent substitute for the normal juice, since it is always

active and easily preserved. Three or four teaspoonfuls are given in carbonated water before or during meals.

The Activities of Extracts of the Intestine.—In addition to the secretin-bearing product procured from the duodenum, extracts of the jejunum and ileum have been made, and considerable experimental work has been done towards establishing their position as therapeutic agents. Enteric opotherapy is available in the treatment of intestinal indigestion, and several preparations are active, especially because of their content of enterokinase. In addition to the trypsin-activating powers of this substance, it has been shown that preparations of this character have a stimulating influence upon the intestinal walls, augmenting the production of the intestinal hormones and kinases, stimulating the production of the succus entericus, and also increasing peristalsis. The addition of extracts of this character to secretin-bearing preparations might be of advantage in the treatment of chronic dyspepsia associated with atonic conditions in the intestine.

Masson[4] believes that there is a series of endocrinous glands in the intestinal wall of man homologous to the islands of Langerhans in the pancreas. At present it is not yet decided as to the physiologic influence of these hypothetical gland areas, but he believes that in pathology these glands may be especially subject to neoplastic growths, particularly the so-called "atypical small-celled carcinomata."

A Motor Excitant in Intestinal Extract.—In their study of secretin-bearing extracts of the duodenal mucosa, in 1904, Enriquez and Hallion[5] noted that during the experiments there was a considerable stimulation of the bowels following injections of these extracts, and that almost invariably after a brief period the bowels were moved and the fæces were often of a liquid nature.

They concluded that the enterokinetic element in the aqueous extract was not identical with secretin, and made a number of attempts to isolate it. They succeeded in securing an active product, but not in definitely isolating the actual active principle. Because of its marked excito-motor action, they called this substance "motiline." It has not been made in commerce, although intestinal extracts, suitably combined, are frequently used to stimulate muscular tone and increase the motor activity of the intestines.

In a later communication these same authors[6] contend that the motiline, which they assert is to be found in intestinal extract, "is the same substance which Zuelzer, ignoring our own researches, has called 'the peristaltic hormone.'" This may be true; but, as will be seen in Chapter X., Zuelzer's hormone is procured from the spleen.

Wieland[7] has since made a series of tests to show the pharmacological comparison between the active principle in intestinal extract and *hormonal*. He is convinced that while these substances undoubtedly have several properties in common, they are by no means identical.

The Depressor Action of Intestinal Extracts.—The characteristic depressor action of intestinal extracts upon blood-pressure has been emphasized by Popielski,[8] and a hypothetical substance, named by him "vasodilatin," is credited with the responsibility for this hypotensive action.

A number of investigators are at work on this and other subjects, and it seems as though a purified hypotensive drug may yet be made from intestinal extracts and used as an antagonist to hypertension. Launoy and Œchslin[9] have isolated an element with a marked hypotensive action, and have called it "depressine." Very small

doses suffice to cause a material reduction in blood-pressure. Heretofore most of the clinical tests have been upon animals.

More recently these authors have reported a new method of preparing depressine from the intestinal mucosa in crystalline and very active form.[10] It may be that this is identical with the β-iminazolylethylamine of Dale and Laidlaw, which will now be briefly considered.

A Remarkable Uterine Stimulant.—A similar, if not identical, substance to the hypothetical "motiline" is the definite chemical product, β-iminazolylethylamine, which may be prepared from intestinal extract, being formed from histidine by the action of certain putrefactive bacteria. This depressor substance has been isolated from intestinal extract by Barger and Dale,[11] who suggest that it is a part of Popielski's hypothetical "vaso-dilatin" (which is supposed to be obtainable from all animal extracts), but differs in that it has no influence upon the coagulability of the blood.

β-iminazolylethylamine has been carefully studied in the Wellcome Research Laboratories by Dale and Laidlaw,[12] who have outlined its principal physiological action. This, in brief, consists of a characteristic depressor action and a stimulating effect upon plain muscle—in particular that of the uterus.

From the statements of these investigators this action seems to be even more marked than that of the extract of the posterior lobe of the pituitary gland, for it is said to be evident in dilutions as high as 1 in 250,000,000.

This substance is more easily made synthetically, and such a product is now obtainable in commerce under the name *ergamine*. The indications for its use are quite similar to those of ergot, and it may be given with advantage where prompt uterine contraction is desired, as in

postpartum hæmorrhage, etc. The dose (hypodermic) recommended is gr. $\frac{1}{65}$ (0·001 gramme).

The Detoxicating Power of Intestinal Extract.—It has been shown experimentally at least that intestinal extract, under certain conditions, exerts a noticeable detoxicating effect.

In 1905, Vidal[13] made an interesting experimental demonstration, before the French Congress of Surgery, on the influence of preparations of the intestinal wall upon the fæcal poisons. A dog injected with very active fæcal extracts died in a few moments, while a second animal survived the same dose of the same poison, to which had been added an extract of the intestinal mucosa. From this experience, Vidal suggested a clinical indication for the treatment of various forms of intestinal occlusion before surgical intervention is made. In this manner, by the destruction of the absorbed poisons resulting from the reflex action of this extract, operative procedures, if absolutely necessary, are made under more favourable circumstances.

Although numerous experiments have been made with intestinal extracts, this therapeutic promise seems to be very limited, and the application of this idea has not been tried in more than one or two clinical cases.

The Hormone Influence of the Appendix.—In our present broadening knowledge of the internal secretory activity of various parts of the body, we are beginning to appreciate the frequent dual activities of various organs. In the literature of the past half-century many references have been made to the function of the vermiform appendix, and these ideas have varied from the suggestion that it is a vestigial remnant of an organ which at one time was useful, to the statement that the appendix is a superfluous, useless organ, the principal value of which is

in the removal! Several studies on the subject have been made, and Salvini[14] has performed a number of experiments which lead him to believe that the appendix normally produces a substance that stimulates the intestinal musculature. This may be a possible explanation of the common clinical observation that appendicectomized individuals are very commonly sufferers from chronic constipation. Quimby[15] of New York, in his radiographic studies, has made some observations which seem to emphasize this position, and one of the conclusions of a recent paper by him intimates that when there is chronic constipation due to delayed or inhibitory action of the bowel, the appendix is usually diseased.

Robert believes that the appendix has an important function in normal digestion, and has found that in certain fish the removal of the appendix materially interferes with digestion. The present author's experiences with an extract of the appendix of pigs indicate that the appendix may also contain an antiperistaltic principle, as the administration of this preparation in several cases had a constipating effect. Experiments are being made with a view to establishing whether or not there are two active principles, the one exercising a stimulating influence on, and the other inhibiting, the motor activities of the bowel.

The whole subject of the regulation of the complex mechanism of digestion has been made intensely interesting by the establishment of the "hormone theory," and it is believed that as the experimental work in this field is standardized and the subject is more fully known, we shall be able to secure a series of very valuable therapeutic agents from various parts of the intestine, to augment or inhibit, as the case may be, corresponding deficiencies or excess on the part of the digestive tract in medical prac-

tice. In the meantime we must be very satisfied to be able to use with such obvious advantage extracts of the pylorus and duodenum, and hope that later other equally valuable preparations may be made available.

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CHAPTER VII

THE PANCREAS AND ITS HORMONE

Is there a Langerhansian Hormone?—The Discovery of the Internal Secretory Function of the Pancreas—The Production of Experimental Diabetes—The Antidiabetic Action of the Pancreas Hormone—von Noorden's Opinion of Pancreatic Insufficiency—Knowlton and Starling's Perfusion Experiment—The Function of the Islands of Langerhans—Langerhansian Disturbances in Diabetes—Compression of the Islands a Cause of Glycosuria—Dock's Summary of the Relation of the Pancreas to Diabetes Mellitus—The Antagonism of the Adrenals and Pancreas—The Differentiation of Pancreatic Diabetes—The Diagnosis of Pancreatic Insufficiency by Adrenalin—The Pancreas Treatment of Diabetes—Clinical Experience with Pancreas Preparations—Pancreas Extract in Hypertension—The Influence of the Pancreas on Phagocytosis.

Much controversy has surrounded the study of the internal secretion of the pancreas and its physiologic action and therapeutic possibilities. Naturally this has made it difficult to establish the therapeutic application of pancreatic opotherapy upon as broad a basis as its well-known and favourable enzyme action upon digestion.

Is there a Langerhansian Hormone? Almost all are now agreed that the "theory" of the dual capacity of the pancreas is a fact, but not all will admit that the term "Langerhansian hormone" is warranted by the findings; for it is still asserted that, while the pancreas may produce an internal secretion, we have no proof that its activities are due to a hormone, nor have we been able to isolate one, and not all are agreed that the islands of

Langerhans are the seat of the elaboration of the internal secretion.

The present author, however, is convinced by personal experience and by a study of a large amount of literature —for the literature dealing with or related to this subject is extraordinarily voluminous—(1) That the term "Langgerhansian hormone" is warranted; (2) that hormone-bearing extracts of the pancreas can be prepared and frequently applied with success in practical therapeutics; and (3) that the presumed pancreas hormone has little or no direct connection with the external digestive secretion of this organ, and hence practically no influence upon alimentary disorders or, more strictly, indigestion.

An attempt will be made to marshal a few of the essential facts which are the basis of the above conclusions, and as the skein is unravelled it will appear that different extracts of the pancreas are very useful in the treatment of certain well-defined disorders of metabolism.

The Discovery of the Internal Secretory Function of the Pancreas.—The internal secretory function of the pancreas does not seem to have been thought of until 1889, when the memorable work of von Mering and Minkowski[1] showed that the removal of the pancreas was invariably followed by the symptom-complex which is called "diabetes mellitus."*

This was a substantiation of the theory put forward twelve years before by Lancereaux,[2] which was based upon his clinical observations in several cases of severe diabetes, in which degeneration of the pancreas was found at autopsy. Lancereaux was the first to use the term "pancreatic diabetes," and, of course, he had to be severely criticized, for others promptly found indubitable

* The study of the internal secretion of the pancreas is inseparably connected with the study of diabetes; hence the major part of this chapter will be devoted to a consideration of this disorder.

cases of diabetes without evident lesions in the pancreas, and still others found grave pancreatic disease with no previous signs of diabetes. Nevertheless Lancereaux's theory is now well established.

The Production of Experimental Diabetes.—While reference has repeatedly appeared in medical literature to von Mering and Minkowski's experiments, it seems advisable briefly to outline their epoch-making results. They made many tests upon dogs, thereby establishing the fact that after complete removal of the pancreas, if the animal survives the operation, diabetes, persisting until death, never fails to appear. If one-fourth or one-fifth of the gland remains, diabetes does not follow; or if a portion of the pancreas containing the islands of Langerhans, and still attached to its arterial supply, is first transplanted under the skin and all the remainder of the pancreas is removed, no glycosuria is produced, but the removal of the transplanted portion is followed by glycosuria.

In this latter experiment, as the digestive secretions of the pancreas are not discharged into the intestinal tract, it seems to prove that it is neither the digestion of the food in the intestines nor injury to nerve structures that is at fault, but that the cause is evidently lack of an internal secretion, presumably from the transplanted portion which contains the islands of Langerhans.*

A number of years later Minkowski[3] was stimulated to repeat his experiments, modifying his technique by performing a two-step operation. He first removed, for later convenience, the splenic portion of the pancreas,

* The enzymes of the pancreas are, however, undoubtedly of value in the treatment of diabetes, if only for the improvement in nutrition and digestion that they facilitate. They also serve to strengthen the functional powers of the pancreas, both as regards its capacity to produce the external secretion as well as the internal secretion.

and did a gastro-jejunostomy; from this operation the dog recovered and gained 1,450 grammes in the following month. The second part of the operation was then performed, at which the pancreas was divided at a distance of 2 or 3 centimetres from its head. The duodenum, to which was attached the head of the pancreas, was then removed, and a cholecystenterostomy performed. Recovery was complete, and the dog remained in good health, showing sugar in the urine for only two days after the operation. At the end of four weeks after the operation the dog's urine was still sugar-free, even though 50 grammes of sugar and 50 to 100 grammes of rice soup formed a part of the daily diet. The remainder of the pancreas was then extirpated, and within a few hours 100 c.c. of urine, containing 9 per cent. of sugar, were excreted.

A similar experiment was performed upon another dog, but a small pancreatic graft was inserted under the skin of the abdomen, with the result that the onset of diabetic symptoms was postponed until the graft was removed.

The Antidiabetic Action of the Pancreas Hormone.—It would be superfluous to relate the numerous confirmatory experiments, or, for that matter, the inevitable dissenting voices. Biedl, with good authority, says[4]: "The results have since been confirmed by means of many hundreds of experiments undertaken by numerous authors, including Lépine, Hédon, Gley, Thiroloix, Caparelli, Harley, Schabad, Cavazzini, Sandmeyer, Selig, Rumboldt, among others." In the latest of his numerous communications on this subject Hédon[5] has conclusively shown that the blood passing from the pancreas has a decided antidiabetic influence. He removed the pancreas from a dog and kept it alive for a month by means of a pancreatic graft; the graft was then removed and glycosuria quickly

appeared. Transfusion from the inferior pancreatic vein of a healthy dog was arranged, and by careful weighings the amount of blood transfused was known. For three hours transfusion was continued, and 300 grammes of blood was passed. Laboratory estimations of the urine showed that at the commencement of the transfusion the sugar percentage was 6·5, and shortly reached 8·1 per cent., in spite of the transfusion, but that very soon the sugar disappeared, and after three hours the urine barely reduced Fehling's solution.

The figures given prove that the pancreatic venous blood has a marked influence on the renal secretion, diminishing the amount of water and its concentration, slightly increasing the urea, and almost completely eliminating the sugar. These experiments confirm Hédon's previous work, and are convincing evidence of the presence of an internal secretion of the pancreas and its influence upon glycosuria.

Von Noorden's Opinion of Pancreatic Insufficiency in Diabetes.—Von Noorden, in his latest book,[6] says: "I think I shall be voicing the opinion of all pathologists when I say that every individual who has a diminished tolerance for carbohydrates, either permanently or extending at least over a considerable period, and thus exhibits the most important clinical symptom of diabetes, must be considered as a subject of pancreatic insufficiency. We need not always expect to find perceptible anatomical evidence, for there may be functional impairment where no macroscopic or microscopic pathological appearances can be discovered."

The pancreas begins the elaboration of its internal secretion before its external secretion is needed. This has been shown by Carlson and Drennan, and later by Lafon,[7] who, in a paper read before the Société de

Biologie, Paris, reports having observed that in a pregnant dog extirpation of the pancreas did not cause glycosuria until the uterine cavity was emptied. It may be reasonably supposed that the production of the internal secretion of the fœtal pancreases was diffused into the blood of the mother and supplied the function of the removed pancreas.

Knowlton and Starling's Perfusion Experiment.—Another most convincing experiment by Knowlton and Starling[8] justifies the idea that the pancreas influences carbohydrate metabolism by an internal secretion rather than by any power which its cells might have of removing or neutralizing toxic substances while the blood is circulating through it. They made observations on the rate at which sugar disappeared from blood that was repeatedly perfused through an isolated mammalian heart preparation (dog), and found that the consumption of dextrose per hour and per gramme of heart muscle was usually less than 1 milligramme when the blood and heart were those of a depancreatized dog, as against 5 milligrammes when the heart and blood were from a normal animal. When the heart was taken from a diabetic animal and the blood from a normal one, the consumption of dextrose for the first hour was still low, but it increased steadily during the next two hours; conversely, when the blood of a diabetic animal was perfused through a normal heart, the dextrose consumption, although almost normal during the first hour, fell off markedly during the second and third.

These results may be interpreted as an indication that a hormone necessary for the utilization of sugar by the tissues is evidently absent in the diabetic blood. This idea is further supported by the observation that the addition of a boiled pancreas extract to the diabetic

blood used in their experiments restores almost to normal its glycolytic power.

The Function of the Islands of Langerhans.*—Being now convinced that the pancreas is concerned in sugar combustion, it may be well to establish the fact that the islands of Langerhans are evidently the seat of the elaboration of the pancreatic internal secretion, and thus explain the term "Langerhansian hormone."

It was in 1895 that Schäfer[11] first offered the suggestion that the seat of trouble in pancreatic diabetes was in the islands of Langerhans, and the autopsy findings reported by a number of writers have confirmed this.

One of the conclusions arrived at by Bosanquet[12] in his Gouldstonian lecture in 1905 is as follows: "Although it is not yet proved, yet it is becoming increasingly probable that the pancreas is diseased in all cases of diabetes mellitus. An increasing bulk of evidence is also accumulating to show that the function of the pancreas, which is in abeyance in diabetes, is normally performed by certain special groups of cells, known as the 'islands of Langerhans,' which are distinct from the ordinary secreting cells of the gland."

Thoinot and Delamarre[13] state that they "have now examined the closed intrapancreatic glands of 167 subjects, and have been able in 130 cases to discover Langerhansian

* Professor R. Lépine, in a personal communication accompanying the manuscript for this chapter which he had just been criticizing, writes: "Unfortunately we are not in accord on one point. I do not admit, and for some time competent authorities do not concede, that the islands of Langerhans are the exclusive organs of the internal secretion (of the pancreas). It is thought even that they secrete very slightly. It is the whole gland which produces the hormone. Please read the reprints which I have marked "—(A),[9] pp. 429-431, and (B),[10] pp. 451-459 and 623-624. One must hesitate to contradict so eminent an authority as Professor Lépine, and the facts *pro* and *con* must be taken as they stand. It cannot be denied, however, that the pancreatic hormone is a substance with a very definite action, and that it offers therapeutic possibilities that are not to be gainsaid.

lesions. We are therefore logically led to regard these forms of diabetes as a clinical demonstration of Langerhansian insufficiency." Lazarus[14] has induced glycosuria and cachexia in guinea-pigs by administering adrenaline and phloridzin during a period of several months. At the autopsies the adrenals and pancreas were enlarged, and the islands of Langerhans had increased both in number and size. He supposes that this Langerhansian hypertrophy is a result of the efforts of the organism to neutralize the excesses of adrenaline that were given. Lombroso could not duplicate these experiments, and contradicts Lazarus's views.

Langerhansian Disturbance in Diabetes.—Opie's[15] experiments at the Rockefeller Institute included a series of the most painstaking post-mortem and pathological examinations. As a result of it he states that—"The study of pancreatic diabetes has shown the relationship of diabetes to lesions of the pancreas and to its various histological structures. If the various lesions to which the pancreas is subject are reviewed, it will be found that those which destroy the islands of Langerhans are almost constantly accompanied by diabetes." At Opie's suggestion, Cecil[16] made a series of autopsy examinations in ninety patients who died of diabetes, and concluded that —"Lesions of the pancreas occur in more than seven-eighths of all cases of diabetes mellitus, and in such cases the islands of Langerhans constantly appear changed, the lesions in some cases being limited to these structures. In half of those cases of diabetes, in which the pancreas shows no changes, the size of the pancreas or the number of islands is less than normal."

In this connection Cammidge[17] also writes: "It is highly probable that the islands of Langerhans are in some way intimately associated with sugar metabolism,

and personally I have no doubt that in at any rate the majority of cases of diabetes, lesions of the pancreas, and particularly the islands of Langerhans, are responsible for the disease." Further evidence is available in quantities, and "the case in favour of the islet theory is steadily growing stronger."[18] The most conclusive evidence has been adduced by Weichselbaum,[19] who, after many years of study, has made the most positive statement on this subject. He states that in *every one* of a series of 183 patients who died with diabetes, in his examination of the pancreas he found distinct and characteristic lesions in the islets; while in an even larger series of control cases. representing many different diseases, no corresponding changes were found. The slight discrepancy between the findings of Weichselbaum and those of Cecil referred to previously is probably due to the fact mentioned by Weichselbaum, that when lesions of the islets occur in young persons, hydropic degeneration is most frequent, and that lesions of this character are easily overlooked, especially if the tissue has not been properly preserved and prepared. This would account for the cases in which the islets have been said to be normal in fatal diabetes, and perhaps may explain why Cecil did not find lesions in the remaining one-eighth of his cases. Weichselbaum's work seems to establish conclusively that the majority of cases of diabetes mellitus are not only of pancreatic, but of Langerhansian origin.

Heiberg[20] has also shown that there is always danger to the island tissue in the pancreas of diabetics. He has studied the islands quantitatively instead of in the usual purely qualitative way.

Compression of the "Islands" a Cause of Glycosuria.—Morris,[21] of New York, believes that many cases of glycosuria are due to pancreatitis caused by the effects

of bacteria escaping from the duodenum, and consequent squeezing of the islands of Langerhans. As soon as the pancreatitis is relieved, the pressure is reduced, and the islands are enabled to resume their functions, and the glycosuria shortly disappears.

Tiberti[22] has shown that an artificially induced hyperplasia of connective tissue in the pancreas ultimately destroys the islands of Langerhans, and so glycosuria results; and Lissauer[23] found in twenty-four subjects with gin liver that the pancreas showed more or less similar changes. His findings confirm those of Weichselbaum in twenty-seven similar cases. The importance of this "gin pancreas" is evident when one remembers the comparative frequency of the development of diabetes mellitus in persons addicted to liquor.

A report by S. A. Scott[24] of Oxford University is of particular interest. He tells of a case of cancer of the pancreas with no previous glycosuria or symptoms of pancreatic internal secretory loss. At autopsy it was seen that the growth had effectively obliterated the ducts and destroyed the glandular part of the organ, with the result that only the islands of Langerhans survived. Opie,[25] in his book, describes and illustrates a specimen in a less advanced state than Scott's.

Dock's Summary of the Relation of the Pancreas to Diabetes Mellitus.—In the Section of Medicine of the Seventeenth International Congress of Medicine, Dock[26] makes the following summary of the foregoing facts: "Now that the relation of the pancreas to diabetes has been carried far towards a conclusion, it is worth while remembering how long it has taken us to reach this stage. Bouchardat very early claimed a place for the pancreas in the pathology of diabetes. Lancereaux and his pupil, Lapierre, tried to show the relation more than thirty

years ago, but sought it in the external secretion. Von Mering and Minkowski looked for it in the internal secretions a decade later; Hansemann soon after insisted on a specific anatomical alteration. In 1895 Schäfer made the pregnant suggestion that the islands of Langerhans are at fault, and in a few years this was confirmed on a large scale by the work of Opie, Weichselbaum, Saltykoff, Hirschfeld, Russell, Heiberg, and many others. There is no question now as to the existence of the insular lesions in most cases of diabetes. . . . It hardly seems necessary here to discuss the meaning of cases of pancreatic disease without diabetes, and of diabetes without pancreatic disease—at least, disease we can recognize anatomically with our present methods."

The Antagonism of the Adrenals and Pancreas.—Attention has already been drawn to the supreme importance of the hormone balance in carbohydrate metabolism (see Chapter III.), and further elucidation of the part that the internal secretory organs play in the regulation of carbohydrate metabolism may be found by studying von Noorden's diagram and descriptive text, which appears on pp. 33 and 34.

A number of experiments have shown that the Langerhansian hormone antagonizes the power of the chromaffin hormone to "mobilize" sugar, or, in von Noorden's words, "the pancreas acts as a brake upon the sugar factory."

Zuelzer[27] was among the first to discover the fact that adrenaline glycosuria could be suppressed by injections of an albumose-free pancreatic extract. Frugoni[28] then confirmed this by showing that pancreas extract had the power of destroying adrenaline *in vitro*. Ghedini[29] (and later other investigators) have shown that a fatal dose of adrenaline, when mixed with pancreas extract, does not

cause death, and is practically innocuous. Pick and Glæsner have also prevented adrenal glycosuria by adding to the adrenaline solution 4 to 20 c.c. of liquid pancreatic extract. The same result, obtained, however, by a totally different experiment, was secured by Frouin and André Mayer,[30] who have demonstrated a diminution of the manifestations of experimental pancreatic diabetes by partial or complete removal of the adrenals.

The Differentiation of Pancreatic Diabetes.—Since the use of hormone-bearing extracts of the pancreas in diabetes is frequently unsuccessful, it is desirable to be able to discern which cases are likely to benefit. Lépine believes that in many cases of glycosuria, and occasionally in non-diabetic disorders, there is a functional insufficiency of the pancreas which is often very difficult to recognize.

Sometimes this is possible only by making a therapeutic test. However, there are several subjective signs which are frequently seen in these cases: marked loss of weight (the French call pancreatic diabetes *le diabète maigre*), serious digestive troubles with steatorrhœa, and an infrequency of soaps in the fæces. These and other tests not mentioned here* are evidence of a general pancreatic disorder, but not necessarily of a deficiency of the pancreatic internal secretion, although it is likely that the manifestations of severe disease of the pancreas will not be confined to its external secretion alone. There is, however, another important procedure which appears to be of considerable promise.

The Diagnosis of Pancreatic Insufficiency by Adrenalin.—The relation of the Langerhansian and chromaffin hor-

* The subject of "the functional diagnosis of pancreatic disease" is exhaustively studied by Pratt[31] in a paper bearing the above title. It is amplified by no less than ninety-six bibliographic references (see also Leech's review).[32]

mones to pancreatic insufficiency, and particularly to the so-called "pancreatic diabetes," led Loewi[33] to suggest a clinical test, which gives fairly constant and useful results. He showed that the instillation of 3 or 4 drops of *adrenalin* (1 in 1,000 solution) into the conjunctival sac causes mydriasis in cases suffering from pancreatic disease. Here it is presumed that the Langerhansian hormone, being diminished or absent, there is an increased excitability of the sympathetic system, due to an excess of the antagonist adrenal hormone; and the minute amount of *adrenalin* is capable of influencing mydriasis. Where this does not take place following the instillation, it is presumed that the pancreas hormone is present, and that this is evidence that the disorder of the internal secretory function of the pancreas is negligible.

This is not an infallible test, however; but as it is quite innocuous and simple, it is recommended in every suspicious case, and especially in all cases of diabetes.

Gandola Quadrio[34] tried this procedure in twenty-five cases in his medical clinic in Rome. Twenty did not respond, and no other sign of pancreatic disorder was apparent. Of the remaining five, four had definite pancreatic disease (two diabetes and two pancreatic tumours), while the remaining case was an epileptic, who, however, showed no sign of alteration in the pancreatic function.

The Pancreas Treatment of Diabetes.—With the formidable amount of evidence to show that the pancreas, and more specifically the islands of Langerhans, are frequently at fault in diabetes, it would seem proper to infer that just as the administration of thyroid extract enables one to replace the lost hormone in athyroidia, etc., so the deficiency of the Langerhansian hormone could be replaced by the administration of extracts of the Langerhansian islets. This is true in a degree; but the

results are not so specific as those that follow thyroid medication in hypothyroidism for several reasons:

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.

The exciting cause of the disturbed hormone balance is not to be neglected, and if it cannot definitely be found (and rarely can this be done, much less can it be controlled), all one can expect to accomplish in this direction is to favour the restoration of the hormone balance as much as possible. This is best accomplished by—(1) The regulation of obvious elements of disturbance, such as indigestion, anæmia, worry, etc.; (2) the regulation of the dietary, so that a minimum of the deficient hormone will be required; (3) the sedation of adrenal overactivity, if present; and (4) the exhibition of preparations containing a maximum of the Langerhansian hormone in doses graded to fit the condition present.

Clinical Experiences with Pancreas Preparations.—As an adjunct remedy in pancreatic diabetes, this method is

* By referring to Chapter XI. it will be found that there are undoubtedly cases of diabetes in which the hepatic hypofunction overshadows any possible pancreatic deficiency.

of encouraging utility. Frequently glycosuria is reduced to a minimum or disappears entirely, and after response to this treatment a wider dietetic range is made possible.

Therapeutic trials of feeding pancreas have been carried out by several writers. Combe[35] found it of good service in many cases, although it did not suffice completely to cause the disappearance of glycosuria, save only in a few cases. He called special attention to the improvement in the nutrition and general condition which was also brought about.

Cowles[36] relates an interesting case in which the ingestion of from one to three raw calves' pancreases daily reduced the daily amount of urine from 7-10 to 2-3 quarts, the specific gravity from 1040-1045 to 1028-1030, and the sugar, although the urine was never entirely sugar-free. The weight was materially increased, during one fortnight 16 pounds being gained. Circumstances caused the patient to stop treatment, and some time later he died from sepsis. The pancreas was found to be a mere fibrous cord. Cowles suggests that the numerous failures with this treatment are due to the administration of too little pancreatic substance, as "few people would be able to eat, even if they could get, the amount of uncooked pancreas taken by my patient."

Zuelzer[27] has reported good results from his preparation, and believes that it is possible to cause sugar, acetone, and diacetic acid to disappear from the urine of diabetic patients by the injection of a specially prepared pancreatic extract. In six cases, between six and sixty-five years of age, treated with subcutaneous injections of extracts of pancreas obtained from living animals at the height of digestion, he reports that the results were uniform and constant, the glucose, acetone, and diacetic acid being always diminished, and usually entirely absent from

the urine in two or three days after injection. In all these cases no change was made in the diet after administration.

It is evident that the pancreas-ferment preparations may have an excellent influence upon glycosuria. 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 reflected not alone upon its external, but also on its internal secretion. Walko[37] noted a conspicuous effect upon the sugar content of the urine, which was seen in a case of glycosuria in chronic pancreatitis. Under *pankreon* medication the excretion of sugar ceased entirely after eleven days, and did not return, although a gradual increase was made in the quantity of food containing carbohydrates.

Rennie and Fraser[38] prepared an extract of the islands of Langerhans of the *Teleostei* (a genus of fish in which Langerhansian islets are sufficiently large to be visible to the naked eye). It was used in five cases of diabetes, with some improvement; but the experiments could not be continued, owing to the limited supply of the extract, and the difficulty of securing it.

Crofton[39] reports good results in a child of thirteen following the administration of a total extract of the pancreas (*holadin*), and in a later paper[40] tells his further experiences. He begins treatment by giving a preparation of secretin*; if no marked improvement is noted, he gives a pancreas extract from which all the coagulable proteins and ferments were removed by heating to 80° C. for three hours. He frequently gives secretin and pancreatic extract together. As to his results, Crofton

* Pochon[41] was probably the first to suggest the combination of secretin-bearing extracts (duodenal) and pancreas extract in diabetes. He believes that by combining these products one can stimulate both the internal and external secretory powers of the pancreas. He reports two cases in which the sugar fell sharply (from 50 grammes to 3 grammes and from 70 grammes to 4·5 grammes per litre), and in other ways improvement was apparent.

writes: "I have seen a sufficient number which were going to the bad on the several lines of treatment improve and resume their usual mode of life, and this on an ordinary full diet. This encourages me in the idea that I am working on the right lines. The patients soon begin to lose their abnormal thirst and hunger, and the wretched feeling of weakness and illness. In some cases the amount of sugar and urine decreases rapidly, but I have never yet succeeded in entirely getting rid of the sugar, although the patient has frequently declared himself well and strong and able for his full quantum of arduous work."

The author's experience has been limited to a preparation of pancreas called *trypsogen*, which is said to contain the internal secretion, besides the ferments trypsin and amylopsin. In several cases of unmistakable diabetes mellitus (with several or all of the usual symptoms—glycosuria, polyuria, thirst, emaciation, and asthenia) the weight has been increased, polyuria quite controlled, and sugar reduced. Occasionally the sugar disappears entirely and, with no further treatment, does not return. A case has been seen in which sugar would return immediately the dosage of *trypsogen* was stopped, and another in which glycosuria returned if the dose was reduced below what apparently was the minimum effective for that patient. No cases of gangrene have been met with personally, but several correspondents have reported encouraging experiences with this treatment, and in the following chapter an excerpt from a paper published by Attix and Rommel[42] records the successful treatment of several severe cases of gangrene.

Certain cases have been found to respond to this treatment in a limited degree, and the sugar is reduced, but persists in small amounts; while, again, not infrequently the results are negative. Quite recently Wynter,[43] in the

discussion on "Glycosuria" at the British Medical Association Meeting (1913), reported having seen good results follow the administration of *trypsogen* in a severe case of glycosuria.

Conclusions.—The evidence is by no means unanimous, nor are the results constant; but it is proved beyond all question that such a condition as the "Langerhansian insufficiency" mentioned by Thoinot exists in many cases of diabetes, and that a possible means of controlling this may be found in extracts of these islands. However, this is but one factor in the control of this complex disease. It seems that pancreas, or preferably Langerhansian preparations, should be added as a part of the routine treatment of all cases of diabetes not definitely known to be due to hepatic disorders, as mentioned previously.

Pancreas Extract in Hypertension.—There are many remedies more active than pancreas preparations for the reduction of blood-pressure, and it must not be inferred from this subheading that the latter are recommended as hypotensive remedies. Occasionally, however, one finds certain cases of hypertension in which there does not seem to be a very marked arterio-sclerosis. The palpation of the usual superficial vessels shows them to be evidently normal, while the sphygmomanometer tells a different tale. In such cases it is quite likely that there is a hyperadrenia, due either to some stimulating action on the adrenals or to a diminution of antagonist hormone from the pancreas. This leads to the suggestion, which has been clinically tried by Ghedini[29] with success, that extracts of the pancreas rich in its internal secretion might advantageously be employed to control these conditions, and if the diagnostic premises are correct, the blood-pressure and associated symptoms are very likely to be lessened by this form of hormone therapy.

The Influence of the Pancreas on Phagocytosis.—It is quite possible that there may be in the internal secretion of the pancreas a factor concerned in phagocytosis and bacteriolysis aside from the influence of trypsin upon bacterial disintegration; and clinical experiences, as well as laboratory experiments with the use of extracts of the pancreas, or better still the Langerhansian bodies, may prove this more thoroughly and conclusively.

In 1913 the author prepared a paper [44] which considered this subject, and it seems best to incorporate it as a separate chapter, which immediately follows this one.

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CHAPTER VIII

THE INFLUENCE OF THE PANCREAS AND EXTRACTS THEREOF ON RESISTANCE TO INFECTION*

The Pancreas is Concerned in the Control of Infections—The Relation of Infective Processes to Pancreatic Disorder—The Opsonic Index in Diabetes—The Action of Pancreas Preparation on Gangrene, etc.—The Relation of Typhoid Fever to Glycosuria—The Pancreatin Treatment of Tuberculosis—Stimulating Phagocytosis with Organotherapy.

THE functions of the pancreas are by no means limited to the production of the ferments for the digestion of proteids, fats, and carbohydrates. While its position as the most important digestive gland is fully recognized, other very important functions of this organ have, during recent years, come to light. We now know that, in addition to the manufacture of its external digestive secretion, the pancreas produces an internal secretion or hormone, which has a very important influence on carbohydrate combustion; while still another important phase of its service to the body as a whole—that of increasing its resistance to bacterial invasion—is now beginning to be admitted. It is to this last that I would direct attention.

The Pancreas is Concerned in the Control of Infections.—That the pancreas plays an important part in preventing or controlling infection has definitely been proved. In the experiments of Hédon,[2] as well as those of von Mering,

* This appeared as an original article in the *Practitioner*,[1] and is reprinted by permission with several new facts which lend additional emphasis to the author's position.

Minkowski,[3] and many others—especially those concerned with the production of an artificial diabetes by extirpation of the pancreas—it was found that to remove the pancreas in one step was almost invariably fatal. The animals did not die of shock or loss of the digestive services of the organ, but from severe sepsis; the wound would not heal. Starling, in his excellent textbook, draws attention to this in the following statement[4]: "One of the main difficulties in the operation of excision of the pancreas lies in the fact that the tissues of a diabetic are extremely prone to infection. It is almost impossible, after total excision of the pancreas, when diabetes has been set up, to procure healing of the wounds without suppuration."

This hindrance to the experiments was soon obviated by the implantation of a small piece of pancreatic tissue, preferably from the tail of the pancreas, in the abdominal wall, either before or during pancreatectomy. This small graft sufficed to preserve the resisting power against infection, and, it may incidentally be mentioned, at the same time prevented the desired outcome of the experiments—the production of an experimental glycosuria. As soon as the animal recovered from its serious operation, it was an easy matter to remove the graft (an insignificant operation, in which danger from sepsis was negligible), with the result that an experimental diabetes was quickly established. This seems to afford evidence of a relation between the internal secretion of the pancreas and the power to overcome bacterial invasion.

The Relation of Infective Processes to Pancreatic Disorder.—There are other ways in which we may give emphasis to this fact. One of the most frequent complications of diabetes, especially diabetes of pancreatic origin, is tuberculosis, a fact that has impressed not a few

clinicians. Montgomery,[5] in a recent paper, gives the results of his study of 117 cases of diabetes, from which he concludes that resistance to the tubercle bacillus is lowered in diabetes, and that a large number of diabetics develop eventually a very acute, extensive, and rapidly fatal form of pulmonary tuberculosis. This investigator notes that when diabetes and tuberculosis occur together, diabetes is usually the primary disease.

The frequency with which diabetics suffer from concomitant infections is well known. Small pimples often rapidly become serious boils, and these in turn sometimes assume the characteristics of carbuncles, and spread with amazing rapidity. Small infections that are considered trivial, or even negligible, may become quite serious in the diabetic, while the frequency of diabetic gangrene is well known.

The Opsonic Index in Diabetes.—While the author is not convinced that the exact estimation of the opsonic index is possible under ordinary circumstances, there is no doubt that there is an index of opsonic capacity even though we may not be able to estimate it accurately. Comparative estimations are better than none at all, and the work of King[6] is of interest in that it shows that the phagocytic capacity is often reduced in diabetes. This writer makes the following statement: "The first examination of ten diabetics to compare the phagocytic activity of leucocytes, on a twelve hours' growth of *Saccharomyces cerevisiæ*, showed their indices to be 0·61, 0·64, 0·68, 0·69, 0·73, 0·805, 0·81, 0·87, and 0·99. We found, therefore, in each of these patients a lowering of the resistance, varying to 0·56 of normal. The one with the index 0·64 had one leg amputated for diabetic gangrene four years ago. The one with the index 0·87 had been taking trypsogen tablets for two months, and said he was much better than he had been."

In his study of the blood-findings in diabetes mellitus, Caro[7] invariably found a reduction of hæmoglobin and a decrease in the number of red cells. Leucocytosis was not present. In twenty-two cases out of twenty-eight there was a lymphocytosis which in fifteen cases was as high as 40 to 70 per cent. These patients invariably suffered from gangrene, tuberculosis, etc.

From this it must be concluded that either the toxicity of the blood in diabetes is the direct cause of the lowered resistance, or that the absence of a certain hormone has a specific influence upon the resistance, in both incidents the trouble being hormonic in origin—in the former case indirectly, while in the latter directly.

These facts seem to establish conclusively that when the internal secretion of the pancreas has been lost, or diminished, either experimentally or from pancreatic disease, there is always a noticeable reduction in the power of the individual or animal to destroy bacteria.

The Action of Pancreas Preparations on Gangrene, etc.—Emphasis of an encouraging nature is lent to these statements by the fact that pancreatic preparations have a marked influence upon infections. A very severe case of diabetic gangrene was recently reported by Attix and Rommel,[8] in which the extensive osseous destruction was illustrated by radiographs. The clinical record is of especial interest, as the medical treatment consisted solely of a pancreatic preparation (*trypsogen*), to which was added ¼ grain of codeine three times a day. Here follows a brief abstract of two cases reported:

"Mrs. L., aged sixty-five, had injured a corn on the great toe. It would not heal. The urine, on analysis, showed 4 per cent. of sugar. Under treatment the sugar rapidly disappeared; but the condition of the toe extended, typical gangrene developed, and eventually the distal half

of the distal phalanx of the toe was picked out with forceps. The wound eventually healed and caused no further trouble. About eighteen months afterward she stubbed the great toe, which became inflamed, but not very sore. The urine was examined, and 8 per cent. of sugar was found. She had stopped all treatment for about nine months, believing herself well. The sugar reached 17½ per cent. (the highest we have ever known), and about one-half of the right foot died from dry gangrene. The line of demarcation was well defined, and the foot became very painful. The sugar was controlled, and operation was advised. The classic operation was done, and Bier's treatment, hot-water bags, etc., applied following it. The flaps failed to unite, became gangrenous, and had to be removed. Operation higher up was advised, but refused. The wound gradually granulated, and at one time both bones of the leg protruded ¾ inch beyond the other tissues. About nine months after the operation, the stump was completely covered with good skin, and caused no trouble thereafter. Three and a half years after the operation the patient died of cancer in the uterus. At no time was there a trace of sugar in the urine. This was a true case of diabetes with many of the classic symptoms, the sugar-content at one time being the highest I [Attix] have met with in many thousands of sugar determinations, but was completely controlled for years.

"Mrs. L., aged fifty-nine, had injured her heel. Gangrene developed, and three-fourths of the heel sloughed off down to the periosteum. . . . On first examination, the urine showed 7 per cent. sugar, and the leg looked as though a line of demarcation were going to form. Sugar disappeared at the end of six weeks' treatment, and has only been present in traces on a few occasions since; the

heel is now entirely covered with good skin, and the patient is doing her housework."

These authors intimate that they might cite several similar cases, and add that "a very inexplicable thing is the healing of these gangrenous areas when sugar is removed from the urine." It would appear that the explanation lies in a special function of the pancreas not hitherto fully recognized. The facts gathered in this paper may help to establish this.

The Relation of Typhoid Fever to Glycosuria.—An interesting phenomenon is occasionally noticed when diabetics suffer from typhoid fever. It is not unusual to find that the sugar may disappear from the urine during the attack. A satisfactory explanation for this is not available, but it may be that in the attempt of the body to re-establish a normal condition in the intestine, the pancreas is stimulated to increased action in order that phagocytosis, notably low in typhoid, may be stimulated, and the infection more thoroughly controlled. At the same time the increased production of the internal secretion of the pancreas suffices to neutralize the antagonizing hormones (see the previous chapter), and to control, for the time being, the glycosuria.

Prendergast,[9] having this peculiar relation of typhoid fever to glycosuria in mind, was interested to find out whether typhoid vaccine would influence glycosuria in diabetes. He gave four patients a dose of typhoid vaccine, varying from 50,000,000 to 100,000,000, at intervals of four days, and in each case the sugar output was very markedly reduced. Later, after discontinuance of the injections, the sugar rose, and at the end of four weeks the vaccine treatment was again begun, and the sugar output was checked.

While this may be of no prospective therapeutic value, it is at least interesting to note the relation between pan-

creatic activity and the production of the opsonins which correspond to the *Bacillus typhosus*.

The Pancreatin Treatment of Tuberculosis.—Several German investigators have been studying the use of pancreatic preparations in the treatment of various infections. Brieger for a number of years has been using pancreatin, given by the mouth, in certain serious diseases, as cancer, tuberculosis, and pernicious anæmia. In a recent article,[10] he cites experiences with several severe cases of pernicious anæmia successfully treated with a combination of pancreatin and arsenic. This author also draws attention to the power of pancreatin to lower the antitryptic index of the blood in tuberculosis, and even predicts a combination of tuberculin with pancreatic extracts as the eventual treatment of that disease.

Strubell[11] of Dresden has shown that the administration of pancreatin in tablet form increased the opsonic index to the staphylococcus, adding that extract of pancreas contains a substance which is concerned in the defences of the body.

Discussing the "New Aspects of Pancreatic Organotherapy," the editor of the *Medical Record*[12] says: "The future may witness the routine use of pancreatin in tuberculosis, in affections of the internal secretions (in addition to diabetes), and in many chronic affections with lowered opsonic index."

The work of Baetzner[13] with pancreatic preparations in the treatment of tuberculosis (concerned especially with the local treatment of surgical tuberculosis) seems to indicate that part of the action of the trypsin is general as well as local. In his conclusions he states: "Even previous to the local changes, a general improvement is observed to follow trypsin injections; lessening and even complete cessation of pain, discharge, and night-sweats, and, chiefly, a very marked improvement of appetite."

Stimulating Phagocytosis with Organotherapy.—Bayle of Cannes has published some remarkable results with spleen extract as a remedy for tuberculosis. This author is perhaps unduly enthusiastic regarding results, which are, after all, mainly empirical; still the nature of these results led the present writer to investigate the matter further. Many statements have been brought to light showing the influence of the spleen upon tryptic digestion.[14] It was learned that the spleen produces a chemical messenger, or hormone, an important function of which is to activate protrypsinogen, thus increasing nutrition and digestion, as well as raising the phagocytic index. Just how this latter is brought about may be explained by Sajous's theory[15]—viz., that the trypsin in the white blood-cells is activated by the splenic and pancreatic hormones, and the capacity of the white cell to digest ingested microorganisms is thereby indirectly increased.

Clinical experience has been gained with the use of a combination of splenic and pancreatic extracts with the idea of combining these important physiological influences. The results have been most encouraging, and the information so far secured seems to emphasize the facts previously stated.

Notwithstanding the convincing physiological study, or even the excellent clinical results outlined above, it would seem that the facts gathered here should serve rather as a stimulus to further practical study than to set this down as a cut-and-dried therapeutic method. The advantages to be gained from the use of pancreatic extracts are certainly not confined to their influence upon digestion, and it would be a pity to withhold from sufferers a means of treatment which is quite harmless, easily administered, and by no means ineffective.

As Leonard Williams has aptly said[16]: "It is time we

set ourselves seriously to examine and appraise the side of the account which is presented by the cultivation of the normal process of resistance to bacterial invasion. . . . Not only are the defences there, asking to be studied, but they afford a subject of inquiry as fascinating as any in the whole range of medicine, and as fruitful in promise as any in the whole range of therapeutics."

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CHAPTER IX

THE FUNCTION OF THE SPLEEN AND THE VALUE OF ITS EXTRACTS

The Broader Functions of the Spleen—Is the Spleen an Internal Secretory Organ?—The Spleen a Factor in the Control of Nutrition—The Spleen a Pancreatic and Gastric Activator—The Metabolism of Iron—Splenic Opotherapy an Adjunct in Infectious Diseases—Malaria and Paludism—Splenic Extract in Diseases of the Spleen—The Influence of Spleen Preparations on the Blood—Increasing Resistance in Tuberculosis—Further Experiences with Spleen Preparations—Dosage.

LIKE numerous other organs, the spleen has undoubtedly a multiple function, and it seems well established that, like the pancreas, liver, or duodenum, it deserves to be classed with the endocrinous organs.

Histologically, the spleen cannot be included with the glands or ductless glands, as its structure does not consist of epithelial cells. Hutchison, in his Goulstonian lecture,[1] mentions the following functions of the spleen: "It is a filter to remove particles from the blood, and also the débris of red and white cells. It is the seat of formation of lymphocytes, and in a lesser degree large mononuclear leucocytes. During intrauterine life it has a part in the formation of red cells, but there is no evidence that this continues after birth."

The same writer further emphasizes his belief in the limited view of the splenic functions in his excellent little book on physiology,[2] in which he says that "the spleen

is usually classed in textbooks of physiology amongst the ductless glands. If by a 'gland,' however, one means an organ with secretory functions, then the term is hardly applicable, for whatever its part in the economy of the body, the spleen certainly does not secrete."

The Broader Functions of the Spleen.—An interesting editorial on the functions of the spleen recently appeared in a leading periodical,[3] from which several paragraphs may be quoted: "An examination of any textbook of physiology will suffice to indicate how utterly chaotic and uncertain have been the views with respect to the probable functions of the spleen. The chief reason for this state of our knowledge lies in the fact that the obvious fundamental experiment designed to test the uses of such an organ has hitherto completely failed to furnish any decisive evidence regarding the real purpose of the spleen."

This does not seem to be quite in harmony with the recorded facts. The editorial continues: "There are numerous records of its experimental removal in diverse groups of animals as well as its surgical removal in man; but either the observations made after splenectomy are entirely negative in so far as any observable perversions of function are concerned, or the evidence is conflicting. Removal of the spleen is certainly not incompatible with the maintenance of life, as is the case in so many other instances of prominent organs which are far less conspicuous in size and apparent importance. There are no detected alterations of metabolism as the consequence of the operation; yet, in spite of all this negative evidence, one cannot help but hesitate to relegate to the pigeonhole of physiologic obscurity an organ which so evidently obtrudes itself in our consideration whenever the viscera are brought to light."

The Question of the Internal Secretion of the Spleen.—Besides the generally admitted facts regarding the physiology of the spleen, there are clear experimental evidences, supported by work which it is not difficult to repeat if desired, that the function of the spleen is not limited to its relation to hæmopoiesis. Some time ago the present author took occasion to make a thorough search of the literature in an attempt to convince himself that there was a previously proven physiological basis for the encouraging results which he and certain others had been obtaining from the use of spleen extract.*

Verzár[5] and Meyer[5a] have recently contributed to the discussion two valuable monographs in which is discussed the importance of the position held by this remarkable organ. Meyer's article is referred to again in Chapter X., and is especially helpful because of its extensive bibliography.

Unfortunately, the most recent books on the internal secretions—notably Biedl's exhaustive monograph—make no reference whatever to an internal secretion of the spleen; and Swale Vincent, in his book, gives this subject only four lines. Possibly these eminent authors have omitted to refer to the spleen because it is not really a glandular organ, and is not presumed to have any other than its well-known hæmopoietic function. Other investigators have expressed their doubt as to the hormone-producing powers of the spleen. Osborne[6] of Yale says: "From a histological standpoint, and from the standpoint of what is known of the physiology of the spleen, and from the fact that men and animals can live after the spleen has been extirpated, it seems doubtful if this organ furnishes an internal secretion. When the

* This was published in February, 1913,[4] and with a considerable number of additional facts forms this chapter.

spleen is removed, the lymph glands do its work. After such removal there is an increase of the lymphocytes in the blood and a decrease of red corpuscles, as well as a reduction of the hæmoglobin, but in a few weeks the blood becomes normal."

Metzner[7] also contests the internal secretory powers of the spleen, but Lépine,[8] in 1914, referring to Metzner's statement, says: "It seems to me, however, that one can hardly contest this action of the spleen." And again: "I have myself made several experiments which appear to me to prove the correctness of this idea."

Whether the spleen produces a hormone or not, and in spite of the fact that a part of its work may be vicariously accomplished by other parts of the body, there is abundant proof that its less evident functions (other than hæmopoiesis and hæmolysis) are worthy of consideration. There is little doubt that—in part, at least—the influence of the spleen is transmitted to suitably prepared extracts, and is therefore available when necessary in the augmentation of these particular functions.

The Spleen a Factor in the Control of Nutrition.—It is evident that in some manner at present little known the spleen exercises a control upon nutrition; but when one sees splenectomized individuals survive, and after several months become quite normal, one is forced to admit that other organs (probably the red bone-marrow and the lymph nodes) supplant the missing organ. Still, it must be admitted that there is not much satisfaction in this conclusion.

Richet[9] indicates that the spleen, by a mechanism which he does not attempt to explain, facilitates the utilization and increases the consumption of foods. Nine dogs were splenectomized, and careful comparative observations were made with nine other dogs as similar as

possible in age, sex, and disposition. This author gives convincing tables, which make it clear that the splenectomized animals ate more and fattened less, and concludes that the missing organ plays an important part in the digestion, assimilation, and consumption of food. This is in corroboration of Bellamy's[10] position, which is outlined in the following pages. This writer expressed his conviction that pancreatic digestion is almost completely destroyed as a result of splenectomy, this digestion being then carried out by the stomach and intestines. The increased need for food in splenectomized animals, and the proof that digestion is not often so perfect with the spleen *hors de combat* or entirely removed, thus shown by experiment, simply emphasize the fact long known to physiologists—that the functions of an organ which becomes diseased or is removed are often taken up by the other organs. All this suggests that the splenic influence on digestion is supplementary.

The Spleen a Pancreatic and Gastric Activator.—Asher and Sollberger[11] believe that the spleen is intimately concerned in the metabolism of proteids, and it will be interesting to revert to the original work along this line, which was begun over thirty years ago. The experimental proof of the above premises concerning the method whereby the spleen favours nutrition was first deduced by Schiff,[12] who contended that the spleen was concerned in the complex function of the pancreas. His original ideas, however, were faulty, and have been disproved, and to his successor, Herzen[13] of Lausanne, must be given the credit of having definitely settled this question. His experiments were most convincing, and prove that the spleen acts as a tryptogene by means of some unknown substance, which it proliferates, and which is carried by the blood to the pancreas. This work has been dupli-

cated by his associate, Bellamy,[14] whose experiments corroborated Herzen's ideas of the relations of the spleen and pancreas. He concludes that " the inactive zymogen granules present in the cells [of the pancreas] receive from the spleen in the form of an ' internal secretion ' the agent with which to elaborate . . . trypsin. The blood carries this product to the pancreas in its solid elements. The jejunal mucosa also furnishes a similar activator, which is produced quite independently of the spleen." Bellamy writes further regarding this: " Without any reference to the possible and perhaps equally important manner in which the spleen acts in other departments of the animal economy, I propose to consider the spleen in the light of a powerful and, indeed, essential factor in the pancreatic digestion of proteids "; and he follows this up with a convincing and comprehensive review of his work and that of his colleagues at Lausanne.

Luciani has caused an extended series of experiments to be carried out in his laboratories at the University of Rome. They demonstrate that the spleen has an influence upon gastric digestion, and as a result of his experiments, which are outlined and diagrammatically illustrated in his book,[15] he concludes that—(1) After extirpation of the spleen the digestive power of the gastric juice is constantly weakened in a greater or less degree; (2) the administration by the mouth of an infusion of congested spleen eight hours before the experimental meal increased the digestive power again for one, two, or even three days.

Further work has been done along this line by Soler and Madero,[16] who are of the opinion that the spleen also plays a part in the production of the gastric enzymes; and Hedin's[17] experiments demonstrated the presence in the spleen of two proteolytic ferments easily destroyed by

heat, the one active in acid media and the other in alkaline. Rettger[18] also has injected directly into the circulation of splenectomized dogs an aqueous extract of spleen, and has demonstrated a definite rise in the trypsin coming from the pancreas, and numerous other studies of the relation of the spleen to pancreatic function have been made by other physiologists.*

The Metabolism of Iron.—In addition to its activation of the digestive juices of the stomach and pancreas, the spleen is said to have a still more extended influence upon digestion and nutrition. Pugliese[19] of Milan has made experiments from which he concludes that the spleen has an influence also upon the composition of the pigments, and is related to the maintenance of the physiologic amounts of iron in the bile as well as in the blood.

"Pugliese has proceeded with the experimental analysis of this peculiar function of the spleen. Interrelations between the liver and spleen have been asserted to exist. The Italian physiologist has therefore investigated the secretion of bile in the same animal before and after splenectomy. The volume of bile secreted after removal of the organ is, if anything, increased; but the output of iron in the fluid is noticeably diminished thereby. This is explicable in the light of the undue amounts of iron in the fæces. Pugliese has further demonstrated a diminution of the iron in the blood, along with the decrease in erythrocytes and hæmoglobin, in the early period after splenectomy. This does not persist very long, however, before a recovery of normal conditions in the blood ensues. The facts confirm what we have earlier pointed out—namely, that with a suitable diet the nutritive outcome of splenectomy need not be in any way unfavourable."[20]

* A number of additional bibliographic references will be found in the author's paper[4] quoted in the bibliography.

This is also the position held by Asher,[21] who believes that the spleen controls the metabolism of iron. He and his pupils at Berne have established the fact that under the most diverse conditions spleenless animals regularly excrete more iron than their normal companions. Evidently the spleen enables the body to retain ingested iron, for the removal of this organ causes an augmented and continued loss of iron in the stools. This finding has been confirmed by Bayer[22] on splenectomized men.

These facts may not be concerned in the consideration of the therapeutic value of spleen extracts, as doubtless the substances which influence iron metabolism may not be present in these extracts; but they evidently explain the reason why certain dietaries are more suitable than others for splenectomized individuals. "If healthy young dogs are maintained for even considerable periods on an iron-free diet, they do not suffer any anæmia unless the spleen has been removed, whereupon a marked diminution in the content of hæmoglobin and the number of red blood-corpuscles promptly ensues. This deficiency is at once made to disappear if meat—a food abounding in iron—is furnished in the diet. . . . The conflicting evidence in regard to the blood-forming functions of the spleen may thus find their explanation in dietary factors. In any event, the removal of the spleen, which is not a familiar surgical procedure, calls for an abundance of iron."[23]

Another factor which must be added to the extended list of the activities of the spleen was first noted by Ott[24] in 1897. The spleen is evidently concerned in the regulation of peristalsis, and extracts of spleen were shown to have a marked effect in exciting the intestinal movements. Considerable time has been devoted to the study of this special action, and the next chapter deals more especially

with what is now called "the peristaltic hormone." It is quite evident, however, that this substance is not identical with those substances to which we have been referring—*i.e.*, the hormones concerned in digestion and nutrition.

Splenic Opotherapy.—Having thus added a little to the textbook information regarding the functions of the spleen, let us collate some of the experiences which go to show that preparations of spleen have a place in rational therapeutics.

An Adjunct in Infectious Diseases.—One would naturally suppose that the spleen must be the source of protective substances, since swelling of this organ frequently accompanies acute infectious disease, and this is considered to be a defensive act on the part of the spleen.

Carpenter[25] has had considerable clinical experience with the use of splenic extract in typhoid fever, and he believes that the good results which he has obtained are due to an influence in restoring the functional activity of the spleen, which, it is well known, is notably disordered in typhoid. Its administration "causes a marked increase in leucocytosis, and otherwise restores its [the spleen's] functions to normal." He used 5 grains of splenic extract three times a day in typhoid fever, and states that this was a means of rapidly and steadily reducing the temperature without undue diaphoresis, and that it ameliorates all the symptoms and restores the patient to the normal.

Malaria and Paludism.—In a more recent article Carpenter[26] also advocates splenic extract as a "real remedy for malarial infection," and explains its action in malaria in the same manner as in typhoid, and goes as far as to state that it produces the beneficial effects of quinine without its bad effects. Incidentally, he also advises the

use of red bone-marrow, which seems to activate the splenic extract in those cases which do not promptly respond to splenic extract alone. This is in corroboration of the experiences of a number of others, who have used spleen in malarial cachexia and paludism with a resultant reduction in the hypertrophy of the spleen, as well as in the other symptoms.

In malarial cachexia spleen may be used to good advantage. Of course, it does not supersede quinine, and must not be counted as destructive to the parasites. Its value lies in its restitutive effects upon the cachectic spleen and blood, reducing the size of the former and increasing both the red and white cells in the latter.

Nouveau's[27] thesis brings together facts which show the advantage of spleen substance over quinine, arsenic, iron, hydrotherapy, etc., in the treatment of paludism. He noted the rather interesting fact that there was frequently slight pain in the region of the spleen two or three hours after the administration of the extract, but that it was shortly followed by a feeling of general well-being. The results were not limited to the moderate cases, but even in most desperate conditions an appreciable amelioration was noted.

Roux and Lacomme[28] showed that extract of spleen increased the resisting power of the blood, and report the disappearance of trypanosomes from the blood following injections of this substance. There does not seem to be any confirmation of this experience.

Splenic Extract in Diseases of the Spleen.—It is well known that various animal extracts are capable of modifying disorders of the corresponding organ. Evidence is adduced elsewhere to show that adrenal extract has been used in Addison's disease, hepatic extract in liver disease, thyroid extract in thyroid disease, etc.; and the results

are said to be due to the partial replacement of the internal secretions of the organ in question, and to a special action, first emphasized by Hallion, manifested by a regeneration of the sound but functionally inactive tissues. This being so, it was natural that extracts of spleen should be tried in several well-known diseases of that organ. Reference has already been made to the use of splenic extract in malarial conditions.

The best results have been secured in the application of this idea in the treatment of splenomegaly, and this in spite of the seriousness of this disorder and its intractable nature.

In a communication made by Paucot,[29] of the French Army Medical Corps, stationed at Hai-Duong (Indo-China), will be found an almost astounding series of experiences. The frequence of splenomegaly in the tropics materially facilitated this writer's tests, and he reports having tried every known method of treatment, including splenectomy. Experiences with this operation lead the author to the conclusion that it is not prudent to remove the spleen. This, however, is a matter for surgeons to discuss. The use of arsenical preparations, iron, ergotine, etc., did not produce either rapid or satisfactory results in the sixty cases so treated.

Of 252 cases in which the spleen was enlarged and there were typical symptoms of splenomegaly, no less than 251 were cured—that is to say, the spleen, which before treatment measured from 10 to 20 centimetres in height, became normal, and was neither palpable nor percussable below the ribs, and the usual symptoms disappeared. The sole remaining case was benefited in a degree.

These results were qualified by a long series of clinical reports from the official Government records, and here

follows as briefly as possible an outline of Paucot's procedure: Fresh beef spleens were reduced to a pulp, and given in doses of 50 grammes each morning; 25 grammes did not give sufficiently rapid results, and more than 50 grammes seemed to be too much. This resulted in an increase in appetite, which, however, was lost and a certain repugnance for food ensued if the dose was raised much above 50 grammes. Translating directly from the article in question, we read: "To sum up, this treatment has given me results incomparably superior to those which I have secured from other methods of treatment. It seems to be able to succeed in every case of chronic splenitis, save only where the spleen has acquired a stone-like hardness, and has become adherent to the diaphragm or abdominal wall. Even then, however, there has been amelioration. The general condition is rapidly benefited. The men are so thoroughly cured that they are able to continue their service, thus obviating a considerable expense and loss of men to the Government."

The Influence of Spleen Preparations on the Blood.—Numerous writers have called attention to the influence of spleen extracts as hæmopoietic reconstructants. All physiologists agree that the spleen is an important part of the hæmopoietic system, although not entirely essential to it. Its influence in the production of leucocytes and its place as an important defensive organ against disease were emphasized by Bezançon[30] in his thesis. Goldscheider and Jacob[31] in 1893 reported that extracts of spleen and thymus produced decided leucocytosis, and showed that this was evidently not due to the nuclein contained in these extracts, for similar experiments with preparations from the thyroid, liver, and kidney, all of which contain relatively large amounts of nuclein, caused no appreciable influence on the white-cell count.

In 1894-95 Danilewsky[32] and Selensky made a study of this subject, and as a result of their experiments they announced that the extract of spleen contained a certain definite substance, not destroyed by heat, which, when used hypodermically, caused considerable increase in the hæmoglobin index (from 7 to 40 per cent.) as well as in the red-cell count (from 10 to 40 per cent.).

Simon and Spillman[33] record encouraging experimental findings, which emphasize the value of splenic extract in modifying the blood-count. Injections of 0·20 gramme of fresh spleen extract caused an increase of both red and white cells, and in one of the cases a red count of 2,988,000 became 6,816,000, and the white rose from 9,400 to 12,800. The therapeutic application of these facts is interesting. Bayle's experiences with the blood-counts following injections of splenic extract are as follows[34]: "When one injects 5 c.c. of splenic extract in a tuberculous individual with a red count of 3,800,000, it will be approximately 5,000,000 twenty-four hours after the injection. A second injection twenty-four hours later will bring the figure to almost 6,000,000. The number then varies during the period of treatment between 5,000,000 and 6,000,000. . . . We have also noted a distinct increase in the number of white cells, the eosinophiles being increased as well as the lymphocytes."

David[35] has also used an extract of spleen in anæmia, clinically confirming Danilewsky's experimental studies. He also found that not only were the blood-findings changed, but the appetite was increased, and there was a corresponding gain in weight and general resistance.

Carnot[36] offers an explanation of the manner in which spleen extracts favour hæmopoiesis. He writes: "We know that in order to stimulate an organ we may employ the extract or pulp of an organ having a synergistic

action. For instance, we stimulate the ovaries by giving thyroid extract. It is therefore conceivable that the bone-marrow may be stimulated by the administration of splenic extracts, and hæmopoiesis thus be regulated."

It is also believed that the spleen exercises an influence on the coagulability of the blood, and in some manner tends to prevent hæmorrhage. A preparation named *stagnin*, produced in Germany, is made from the spleen of the horse. It is a liquid preparation, and in its production the spleen substance has been subjected to autolysis. The dose is 1 to 2 c.c. subcutaneously. Landau[37] has used it with success in various hæmorrhages, and reports especially good results in menorrhagia.

A remarkable coincidence was noticed by Landau, which is worth mentioning. He found that in cases of multiple cancer which came to the autopsy-table, even though several organs—lungs, liver, kidneys, etc.—were studded with miliary carcinomatous nodules, the spleen was invariably free from them.

Increasing Resistance in Tuberculosis.—It has been proved that the protective powers of the organism are dependent in part upon the presence in the leucocytes of a certain amount of active trypsin.[38] It is also believed that phagocytosis is virtually digestion of the enveloped bacteria by the white blood-cells, and, further, that trypsinogen passed from the pancreas into the blood is activated by the splenic hormone, and the active secretions are then utilized by the white cells. Whether this sequence of events occurs regularly or is brought about by spleen substance is not yet proved, but the literature contains much substantial evidence that resistance to infection, especially in tuberculosis, may be facilitated by the administration of preparations of spleen.

One of the pioneers in this fruitful field of investiga-

tion is Bayle of Cannes, to whom the author is indebted for the stimulus which has caused him to make clinical tests as well as an exhaustive study of the literature on this subject.

While clinical reports in the application of this idea are still comparatively few in number, a limited personal experience, coupled with that of several correspondents in Great Britain, the United States, France, Italy, and Russia, convinces me of its importance. Since tuberculosis is essentially a wasting disease, a vital part of its treatment is the attempt to increase the nourishment of the body, thereby enhancing its resisting powers. It certainly seems as though the facts already brought forward substantiate the value of splenic extract, and one cannot but be convinced that this method of treatment is worthy of much more extended trial. A preparation of the extracts of spleen, liver, and pancreas[39] has, to the author's certain knowledge, been a factor in favouring the nutrition of a number of consumptives in whom the nutritional element was the most discouraging feature.

For nearly twelve years Bayle has used spleen preparations in tuberculosis, and in his communication, read before the International Congress of Tuberculosis at Rome, April, 1912, he concludes: "I feel authorized by my results to call splenic opotherapy a specific treatment for tuberculosis. It is specific from the therapeutic viewpoint, because it modifies the soil, rendering it less suitable as a medium for the culture of the bacillus of Koch. It is specific from the practical viewpoint, because it manifests all the function and rapidity of action of a specific medication. Employed in convalescents, it prevents tuberculosis by increasing the mineral content of the tissue (*en rémineralisant le terrain*). Employed in confirmed cases of tuberculosis, it cures them."

In an earlier communication Bayle[40] refers to "150 cases treated by me in which I have noticed 146 showing the unquestionable and rapid effects of the treatment. Among those which I have been able to follow for a length of time sufficient to acquire some conviction, I note 75 per cent. of cures, some of which were in a very advanced stage, and regarding which I had no hope to begin with."

In no disease have so many and such varied remedies been recommended as in tuberculosis, and the mere number alone is evidence of their unsatisfactory results. Time and again our hopes have been raised, to be as rudely dashed to the ground. One therefore accepts with considerable reserve such enthusiastic statements, no matter how thoroughly they may be backed up by clinical results. While many have considered Bayle's experiences as "too good to be true," there is no doubt that a more general trial of spleen preparations in tuberculosis will be both interesting and profitable.

Bayle's method is of interest, for he has secured indubitable results. He prepares an extract of pig's spleen, which is called *colloidogénine*, because he believes that its action is connected with a hypothetical capacity of this organ to maintain, by means of an internal secretion, the principal mineral elements of the blood in a colloidal state —the so-called "colloidogenic" function.*

* Bayle's theory is this: The blood contains the mineral elements in two forms—(1) Those in a colloid state suitable for cellular appropriation, and thus not suited for elimination by the kidneys; and (2) the mineral cellular wastes, which are dissolved in the plasma, and are destined to be eliminated. If the colloid elements lose their colloidal form, they are promptly eliminated, and a condition of demineralization obtains. The capacity to maintain the mineral salts in a colloidal state is evidently of considerable importance, and according to Bayle, seems to belong to the spleen. Bayle states that he has always found that splenic opotherapy quickly reduces an excessive elimination of phosphates in the urine All of this deserves to be tested experimentally and clinically.

He injects the contents of a 5 c.c. ampule into the buttock each day for twelve days. Then, after a rest of eight days, he commences another series of twelve daily injections, followed by another rest of eight days, and so on until the results warrant discontinuance of the treatment. He reports having given over 4,000 such treatments, with no inconvenience.

By mouth he gives an elixir, the strength of which corresponds to 25 grammes of fresh spleen to each tablespoonful. Four tablespoonfuls are taken each day, one at each meal. Bayle has also given 100 grammes per day of spleen pulp in jam, and suggests the cruder method as available for the poorer classes, as it is less expensive and just as efficacious.

Hypodermic and oral administration may be combined, and the dosage above is followed—*i.e.*, 5 c.c. hypodermically and 25 grammes four times a day in elixir, syrup, or raw in jam, etc.—thus obtaining a maximum of activity and rapidity of response. In his most recent paper at this writing (December, 1913), Bayle concludes[34]: "To date I have treated several hundred cases of tuberculosis—pulmonary, osteo-articular, and glandular. The results have been: 100 per cent. cure in primary pulmonary tuberculosis, 75 per cent. cure in all cases (including the cachectic, advanced cases), remarkably rapid cure of white swellings (*tumeurs blanches*) (treatment lasting from one to eight months), cure of tuberculous glands in from fifteen days to two months. This treatment, which is perfectly innocuous, gives results comparable for rapidity and constancy to those which follow the so-called specifics."

Further Experiences with Spleen Preparations.—Quite recently van Stockum of Rotterdam[41] has been experimenting with an extract of spleen which has previously

been exposed to the Röntgen rays. He reports 3,000 treatments, which show that the method is harmless, and that it causes an early change for the better in many cases, especially of surgical tuberculosis. He first transplanted healthy splenic tissue under the abdominal skin, and rayed it daily with encouraging results; and later, to obviate the necessity of the operation, after several attempts, he obtained a liquid which gave excellent results without producing toxic symptoms when injected daily in doses of 20 c.c. Four patients were treated with the mixture of splenic tissue in a solution of hydrogen peroxide, and then subjected to X-ray treatment. Three of these were cured, and the fourth was improved. Another series of experiments was undertaken with the preparation obtained through repeated precipitation of the fluid above described. The last precipitate contained what van Stockum believes to be the active principle, and this proved more powerful than any of the preceding substances used, causing marked improvement after two injections. This last treatment was applied in seven cases, and has given encouraging results in every one. For five or six days 20 c.c. are injected daily, and van Stockum believes that he has obtained a permanent cure by this method.

To test the results of van Stockum, Bayle,[34] acting upon the advice of Professor Lépine, made a series of daily blood-counts in a number of cases, half of which were treated with Bayle's aqueous extract (*colloidogénine*) and the other half with extracts which had been irradiated according to the method of the Dutch writer. The results were the same in both series, and it is concluded that van Stockum's results were due to the virtues of the splenic extract itself, and not to changes brought about by the influence of the X ray upon it.

Schröder,[42] Superintendent of the Neuen Heilanstalt für Lungenkrankheiten in Schömberg, has carried out many tests which show that the spleen is a defence organ against tubercle infections. It was noticed that rabbits and calves show a relatively great resistance to tubercle infection, and Schröder concluded that the spleen of these animals is especially rich in the hypothetical defensive agent, and would increase the resistance if introduced into an infected organism.

Tuberculous human sputum was administered to guinea-pigs or subcutaneous injections were made of the sputum or of fresh cultures of human tubercle bacillus. An extract was prepared from the spleens of animals immunized to tuberculosis, and was given hypodermically. Some of these animals received injections before and some after the inoculations. The dose of the extract was in all cases regulated by the body weight of the animal. The immunizing effect of the extract was obvious, insuring a longer duration of life and milder lesions in the animals treated as compared with the control animals, in which the typical lesions of experimental tuberculosis were found.

In the animals treated with splenic extract the tuberculous foci in the lungs showed a marked tendency to fibrous healing. Wherever caseation was found, it was in a retrograde state, indicating attempts at healing.

In a further communication Schröder[43] and his associates report that "a certain immunity follows injections of splenic extract, and the resistance to tuberculous infection is manifested by connective-tissue organization of the tuberculous foci. Tubercle bacilli lose their virulence when kept in contact with splenic extract. Direct bacteriolysis was not observed. Splenic extract does not diminish the antigens of O.T., no antituberculin being found in the serum of animals treated with splenic extract."

Some of Carrel's[44] experimental work at the Rockefeller Institute seems to give weight to Schröder's remarks concerning the influence of this treatment upon fibrous encapsulation. Carrel advances the startling view, which is backed up by the most extensive experiment, that certain tissue extracts have the power to activate *in vitro* the growth of connective tissue. While he found that the extract of chick embryos was the most active preparation, extracts of adult spleen were almost as active, while kidney and heart extracts were much less active, and extracts of connective tissue or blood-cells were almost without influence. Carrel intimates that these discoveries "may be indirectly useful by leading to the discovery of some of the factors determinating the growth of tissues and of the unknown laws of cell dynamics, and may ultimately throw light on the mechanism of the cicatrization of wounds."

Strangely enough, spleen preparations have been advocated in Great Britain for the treatment of certain phases of insanity. Clark[45] used them in asthenic cases, with good results both on the general and mental condition. Their principal influence was upon the weight and blood-count. Confirmation of this is given by Bois and Kerr,[46] who pointed out that splenic extract is often useful in such cases, especially when associated with thyroid extract, where indicated; but this is not generally admitted.

Quite a number of other references regarding the influence of the spleen and its hormone may be found, and interested readers are referred to the writings of Patricelli, Liverato, Grimana, Foà, Maggiore, Salomon and Halvron, Lépine and Lyonnet, and Williams.

Dosage.—Splenic extract is practically non-toxic. Simon and Spillmann[33] report that a series of injections

of 2 to 4 c.c. in frogs varying in weight from 80 to 92 grammes were not accompanied by the least trouble. The dose varies considerably. Paucot found, as already noted, that more than 50 grammes of chopped spleen were not well tolerated, while Bayle's dosage is twice this. Dried extracts are not so nauseous, and, according to Carnot, may be given in capsules or tablets containing 1½ grains (0·1 gramme) or more, four to ten tablets being given daily.

The statements preceding and a study of the literature referred to in the bibliography should convince even the confirmed sceptic that the splenic functions have an extent and importance far beyond their immediate connection with the blood. There can be no reasonable doubt that the spleen has a very important influence upon digestion, nutrition, hæmopoiesis, and resistance to infection, and that splenic extract is a valuable remedy in the treatment of those conditions in which malnutrition, anæmia, and infections are important factors. While the author does not for one moment consider splenic extract a panacea, it undoubtedly facilitates an increase in weight and resistance in many cases, and should be regarded as a remedy with a reasonable basis and of considerable therapeutic promise.

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CHAPTER X

THE PERISTALTIC HORMONE OF ZUELZER

The Hormone Control of Enterokinesia—The Action of the Peristaltic Hormone—The Relation of the Spleen and Intestines—Concerning the Depressor Action of Hormonal—Combining the Peristaltic and Infundibular Hormones—The Treatment of Chronic Constipation—The Control of Intestinal Paralysis—The By-Effects and Dangers of Hormonal—Neohormonal—The Usual Methods of Administration—The Oral Administration of Hormonal.

As far back as 1897 Ott[1] of Philadelphia showed that extracts of the spleen when injected into animals had a decided influence upon intestinal peristalsis. This seems to be the first indication of the presence in this organ of a substance which influences the natural alimentary movements.

Ott's discovery remained unappropriated by the profession until Zuelzer and his associates rediscovered it in 1908,[2] and with the unfolding field of hormone action before them, the term "peristaltic hormone" was applied to the organic active principle which is believed to be concerned in establishing normal intestinal peristalsis.

The Hormone Control of Enterokinesia.—With the facts before him concerning secretin action, and the convincing results of experiments with other substances of similar action, it naturally occurred to Zuelzer that the muscular activities of the intestinal walls were probably not controlled solely by nervous impulses. By analogy this investigator's hypothesis was that the presumed "peri-

staltic hormone " must be found in the stomach. After some time he succeeded in preparing extracts of the gastric mucous membrane that showed a marked action upon the intestinal peristalsis of the animals experimented upon. It was further ascertained that this hormone was produced in the stomach and duodenum in the course of normal digestion, the greatest quantities being made at the height of digestion, carried off by the blood, and stored up in the spleen. It can be extracted from the mucous membrane, but before long the whole of this substance that was used in the numerous experiments was prepared from the spleen of cattle because of the comparatively greater quantities secured, and to-day this organ is the source of the trade preparation "*hormonal*," which is becoming generally used.

As a result of animal experimentation it was found that the peristaltic hormone, when introduced into the blood, caused a vigorous stimulation of atonic intestinal walls, and that its influence extended to conditions bordering on paresis—where intestinal motion was practically gone. It was presumed that in this hormone we had a cathartic which, acting through the blood, could be given directly into the circulation, and this surmise has fortunately proved to be well founded.

The Action of the Peristaltic Hormone.—Just how the peristalsis initiated by this hormone is brought about is not absolutely known. It may be due to an activating influence upon the nerves of the area concerned, similar to the now well-known action of the chromaffin hormone on the sympathetic system. The hypotensive action of *hormonal* is quite constant, and as likely as not is a factor in bringing about its influence on peristalsis, for evidently the vessels of the intestines are temporarily dilated and gorged with blood, while the superficial vessels are corre-

spondingly depleted with the accompanying, though evanescent, fall of blood-pressure. Zuelzer himself has noted in the records of his experiments that changes in the blood-pressure are a part of the normal physiologic action of the peristaltic hormone, and are accompanied by a very strong flow of blood to the intestine. Probably the action is a combination of both the above, the latter being in the predominance.

Zuelzer[3] suggests two theories in an attempt to account for the effect of this substance: (1) In chronic constipation there is a complete absence or an insufficient production of the peristaltic hormone, and its introduction stimulates its normal elaboration; and (2) the initial starting stimulus to peristalsis is brought about by nervous impulses, the introduced hormone having exerted an action on the abdominal sympathetic ganglia.

The Relation of the Spleen and Intestines.—Meyer[4] of Cologne remarks that intestinal atony not infrequently follows splenectomy. After a time the symptoms disappear, the presumed peristaltic action of the spleen having been taken up by the other organs. He tried *hormonal* in several cases of meteorism and intestinal paresis which followed splenectomy, and obtained striking results. He also has done some interesting experimental work. Six rabbits of one breed were splenectomized, some fasting and some after a full meal. There was a visible swelling of the abdomen of all the animals during the first two days, which otherwise were quite well. On the third day a part of the animals were reopened in a bath of Ringer's solution at body temperature, and 2 c.c. *hormonal* was injected. It was followed by an intense peristalsis. Other animals were examined with the *X*-rays after the administration of a bismuth meal. Here *hormonal* injections showed after ten seconds " a real uproar

in the visible bowels." Finally Meyer studied the free spleens of four rabbits after a *hormonal* injection. The organ was filled with large quantities of blood, and its flat form visibly swells, while almost at the same moment the peristalsis begins.

Concerning the Depressor Action of Hormonal.—Not all investigators admit the basis of Zuelzer's work and that of those who have confirmed his position. There must always be dissenters. The Russian investigator, Popielski,[5] whose pessimism regarding hormones has already been referred to (p. 61), attributes the action of *hormonal* to the vaso-dilator substance (" vaso-dilatin "), which he believes to be present in all internal organs, and which primarily reduces tension, and shows a secondary effect on peristalsis. Popielski's position is, in a degree, shared by Dittler and Mohr,[6] who lay stress upon the hypotensive action of this hormone. They report experiments upon seventeen animals (thirteen cats, one dog, three rabbits), in which peristaltic stimulation was found in only four of the cats, and was stopped by adrenaline injections. These same authors report in a later paper the results of further research, which confirm their previous statements that the peristalsis-producing action is merely the result of the drop in blood-pressure caused by the *hormonal*. When the injection is made very slowly, it does not induce peristalsis in animals. They found that injection of chloral had a pronounced effect in inducing peristalsis in rabbits, even in doses of less than 0·05 gramme per kilogramme. This effect never failed, and it is possible that some of the action attributed to *hormonal* may have been due to the preliminary injection of chloral in the experimental tests of the remedy. This position does not seem to be tenable, for the depressor action referred to by these writers lasts for a very short time during and immediately following

the injection, whereas the therapeutic effect is not set up until five or six hours later. Then, too, the persisting effects of this treatment cannot possibly be explained by a passing drop in blood-pressure.

Combining the Peristaltic and Infundibular Hormones.—In a personal communication to the author Zuelzer writes: "I have personally proved on men that the effects of *hormonal* are not due to the drop in the blood-pressure. I secured a prompt effect in a case of reflex paralytic ileus with a dose of *hormonal* to which a very small quantity of *pituitrin* was added. This amount is, of course, so small that alone it has no effect on the bowels; but not only did the injection cause no fall of blood-pressure, but an actual increase of 10 to 15 millimetres." Here, it seems, is an excellent suggestion, no reference to which can be found in the literature.* It is suggested that to 15 or 20 c.c. of *hormonal* $\frac{1}{4}$ to $\frac{1}{2}$ c.c. of *pituitrin* be added, and the whole given intravenously with 10 to 20 c.c. of warm saline solution.

The Treatment of Chronic Constipation.—The peristaltic hormone is not simply an organic cathartic. Its influence upon constipation is quite different from the well-known and varied effects of calomel, saline aperients, or cascara. Nor should it be used as a remedy for constipation generally, for there are some forms (notably spastic constipation, in which there is already an overstimulation of the intestine, and volvulus or organic obstipation in which mechanical factors are present) in which it is manifestly contra-indicated.

Its application has been largely left to the intractable cases of *obstipatio chronica*, in which evacuations of the bowels are secured at intervals of several days, or even

* After the proofs of this were received, the author noticed a reference to an article[6a] the title of which indicates that others have been considering this subject.

weeks, and then only by recourse to drastic medicinal or mechanical means. In such cases good results have been secured, and since, when the initial dosage has once started the bowel movements, it does not have to be repeated as the ordinary cathartic drugs have, it seems that the fundamentals of its therapeutic usefulness are sound. There are numerous reports in which seriously chronic cases were enabled to find the necessary but missing impetus, and peristaltic action was started and continued for months. As Saar[7] has said, it is as though a stationary pendulum, as a result of one single push, had again resumed its motion.

Numerous cases responded to a single dose, while others required two or three injections at later periods, the intervals between the doses varying from a few days to several months. It should be noted that the commencement of the effects of the intramuscular injection in chronic constipation varies, and may not be manifest for two, three, or even five days. Not all cases respond. Zuelzer reports 71 per cent. of lasting successes and 29 per cent. of failures.

The Control of Intestinal Paralysis.—The other special series of conditions in which this treatment is effective are those in which there is a stoppage of peristalsis and the immediate control of intestinal paresis is desired. This may be due to operative shock, or may accompany severe intestinal infections (appendicitis) and peritonitis. A number of surgeons have reported spectacular results following single intravenous injections of this hormone preparation, and there can be no doubt that this treatment was the principal factor in saving life.

There is already quite a large bibliography on this subject, the principal papers being those of Zuelzer,[2, 3, 8] Saar,[7] Henle,[9] Arnaud,[10] Lenormant,[11] Aaron,[12] and Hesse.[13]

The By-Effects and Dangers of Hormonal.—Several untoward results have been recorded in the literature as due to the action of *hormonal*. Among these are a transient rise in temperature (which may reach from 103° to 105° F. for a few hours only), the so-called "hormone fever," a slight headache lasting from a few hours to a day, and occasional nausea. Following intramuscular injections there has been more or less local pain, and, rarely, induration, but these are not uncommonly found with intramuscular injections of any preparation.

During 1912 several more serious cases were reported,[14] which have thrown doubt upon the harmlessness of this preparation, three or four of them having been fatal. The main detrimental result was collapse following the injection. As a result of this, several articles and editorials appeared, condemning more or less forcibly the whole treatment, while the manufacturers and Zuelzer set themselves to discover if there was not something that could be remedied.

Neohormonal.—Extensive investigation revealed the presence of a hypotensive albumose, which since then has been removed, and all preparations are now tested both chemically and experimentally. In a personal communication to the author regarding the action of this preparation Zuelzer writes: "We intend to call this *neohormonal*. . . . I have no longer observed any rise of temperature following intravenous injections of even 40 c.c., but after intramuscular injections a slight rise is sometimes still observed. I believe that this is caused by the absorption of mechanically damaged muscle tissue."

Hesse[13] tells of encountering collapse after using *hormonal* in 1912, but in a paper relating his experiences with the purified preparation[15] he refers to "seven cases

of severe intestinal paresis treated for three or four days with all the other usual measures without results. *Hormonal* was used as a last resort, and its effects were remarkable. In no case did it fail. . . . A case of collapse has not been seen. . . . The new *hormonal* has given excellent results, and manifests nothing short of an extraordinary life-saving influence."

The Usual Methods of Administration.—With a carefully applied technique this more recent preparation causes the same beneficial therapeutic result with a minimal hypotensive action. One must observe, however, certain precautions in the administration of *hormonal*, and the following method of administration is advised: *Intravenously :* Advised for hospital use only and for acute paretic conditions. Dose, 20 c.c.; for children proportionately less.* The liquid is first warmed by immersing the bottle in water at 110° F., and held as nearly as possible at body temperature during the injection, which is made drop by drop into the median vein, allowing fifteen to twenty minutes for the entire 20 c.c. to enter. *Intramuscularly :* Dose, 20 to 40 c.c. for chronic constipation. The liquid is warmed to body temperature, and the injection slowly made from 3 to 4½ inches into the gluteal musculature (not the fatty tissues), one-half of the dose on each side. One or two tablespoonfuls of castor oil should be given as a lubricant to assist in the dislodgment of impacted fæcal masses from the large intestine. Aseptic precautions are, of course, carefully observed.

It has been suggested that injections be given in the early morning, and the patient confined to bed during the day to obviate rise of temperature. The administration of opiates shortly before and after *hormonal* injections

* Henle[9] reports the successful use of 1 c.c. in an infant four months old.

should be avoided, as they oppose the desired physiologic action.

The Oral Administration of Hormonal.—Until recently the peristaltic hormone has been recommended to be given by intramuscular or intravenous injection. The idea (proved time and again to be erroneous) that practically all organic remedies are destroyed in the stomach has doubtless hindered a wide use of this and other animal remedies. The first reference to the administration of *hormonal* by mouth is a paper by Achard.[16] In it he states that—"The difficulties attendant on the intramuscular injection of *hormonal* in cases of constipation led me to try oral administration. I was further drawn to this method by the argument that the peristaltic hormone exercises its effect directly on the alimentary tract. *Hormonal* was given to four persons, all of whom suffered from severe constipation. Two of these, men aged twenty and fifty respectively, derived no benefit whatever. The results in the other two patients, however, were most remarkable. These were both women. The first, aged fifty-four, unmarried, had suffered from constipation nearly all her life. A dose of 20 c.c. was given; slight discomfort was felt for a day, and four days later a spontaneous evacuation took place. On each of the subsequent days the bowels moved freely, until the motions gradually settled down to one every second day. This continued practically for nine months, and at the time the article was written she was still fairly regular, only the one initial dose having been given. The second female patient, aged thirty-six, married, gave similar results, which lasted for about two months, after which the effect gradually wore off."

In concluding his interesting paper, Achard writes: "If it can be established that *hormonal* can exert its

favourable action upon the peristalsis on being introduced directly into the stomach, and if this action persists at least fairly well, even if it is not as intense or as prolonged as after intramuscular or intravenous injection, our means of overcoming constipation with all its harmful consequences, and with all its immense power to produce injury to the organism, will have been strengthened materially. The important point to my mind is that if *hormonal* can be established as an efficient treatment for selected cases of constipation, we have in this preparation a physiological remedy the use of which is *a priori* far preferable to that of any laxative or cathartic drug."

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CHAPTER XI

THE VALUE OF LIVER EXTRACTS

The Numerous Functions of the Liver—The Hormone Control of Hepatic Action—The Active Principle of Cod-Liver Oil—The Fundamental Value of Hepatic Extracts—The Treatment of Digestive Disorders—Stimulating Liver Inactivity—Hepatic Cirrhosis—The Influence upon Hæmorrhage—A Reported Action upon Phlebitis—Possible Usefulness in Icterus—A Consideration of Hepatic Diabetes—Augmenting Elimination in Gout—In Anæmia and Tuberculosis—Combining Biliary and Hepatic Extracts—Dosage and Administration.

THERE can be no question that the administration of suitable extracts of the liver renders very real service in the treatment of several affections. While the scientific application of this idea has been in use for fifteen or twenty years, there are evidences that this therapeutic procedure is extremely old. It is recorded that Dioscorides treated hepatic dropsy by administering a preparation of the liver of hedgehogs which had been dried in the sun, and Galen extols the use of wolf's liver as a means of treating icterus.

The Numerous Functions of the Liver.—Many physicians still consider the main function of the liver to be that of bile production. On second thoughts, they remember its capacity to manufacture and store glycogen, as well as its influence upon the genesis of urea. It is granted that these several and widely divergent functions are of extreme importance, but the less well-known

detoxicative action of the liver and its antibacterial powers are also worthy of consideration.

Our knowledge of the hepatic functions is broadening, and it is maintained that, in addition to numerous ferments (proteolases, nucleases, adinases, oxidases, etc.), and the well-known bile salts (sodium glycocholate and sodium taurocholate) and pigments (bilirubin, biliverdin, and urobilin), the hepatic cells also produce other chemical substances of the nature of hormones.

Apart from its better-known work, then, the liver has several other functions. The rôle that the administration of liver substance or extract plays depends upon its power to influence these "lesser functions," which have been conveniently classified under the following four heads:

1. The regulation of nitrogenous metabolism, and especially the production of urea.

2. The regulation of the normal sugar content of the blood and the preparation and storing up of glycogen.

3. A reported noticeable influence upon the coagulability of the blood.

4. The destruction of toxins and the regulation of toxæmia both by inhibition of production and by destruction of completed substances resulting from intestinal fermentation and putrefaction.

The Hormone Control of Hepatic Action.—With our present knowledge of the effects of the hormone secretin (see Chapter V.) and the factors concerned in the production of various digestive ferments, it is quite reasonable to suppose that similar factors influence the work of the liver.

Luciani[1] refers to the fact that all nerves to the liver can be divided without causing arrest of the biliary secretion; also that all branches of these nerves can be excited

successfully without influencing the flow of bile either by accelerating it or by stimulating a suspended flow. Evidently, then, the physiology of the secretory function of the liver is quite similar to that of the pancreas and other glandular organs, and in spite of some objections that have been raised by physiologists to the "secretin theory," there seems to be reasonable ground for the assumption that hormones materially influence the function of the liver.

The study of the functions of the liver has been carried on for many years, and as yet we are still very much in the dark as to how this remarkable organ performs its equally remarkable work. The supposition that the liver itself is a source of hormones has been mentioned by several writers, and the fact that its detoxicating function is conceded to be greater than that of any other organ seems to give weight to this suggestion.

The Active Principles of Cod-Liver Oil.—In this connection a word or two regarding a well-known and universally used liver preparation may be in place. In his consideration of "The Therapeutic Promise of the Internal Secretions," Williams[2] says: "There can be no doubt of the superiority of cod-liver oil in fortifying the tissues against the bacillus of tuberculosis, neither can there be any doubt that cod-liver oil is different from all other oils in this respect. Now, it is evident that its superiority is due to the fact that in addition to the oil it contains the internal secretion of the liver of the fish. It is not, of course, to be supposed that this internal secretion enters at once into the human *liquor sanguinis*. The way in which it acts must, in the present state of our knowledge, be a matter of mere conjecture. Inasmuch, however, as we know that certain of the internal secretory glands exercise certain antagonisms to certain others, so

that an excessive secretion in one will provoke an increased activity in one or more of the others, 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. Some of these internal secretions are subtle entities, and it is a significant fact that the darker and more crude the cod-liver oil, the more efficacious is it. The refining process deprives it of many of its virtues, whereas the dried extract of the cod's liver is almost as active as the crude oil."

Quite recently Iscovesco[3] has published some experimental work which shows the soundness of this position. He is convinced that the special properties of cod-liver oil are due to the lecithides which it contains, and that while the fat is useful, it is no more so than vegetable fats. Some of the figures from his experiments are interesting. He treated a large series of animals for four months. To some he gave cod-liver oil (*a*), to others cod-liver oil from which the lecithides had been removed (*b*), a further series received olive oil (*c*), and others olive oil to which was added 0·5 *pro mille* of the lecithides extracted from cod-liver oil (*d*). There were, of course, a number of control animals (*e*). Here are the average weight increases recorded: (*a*) 55 per cent., (*b*) 27 per cent., (*c*) 33 per cent., (*d*) 56 per cent., and (*e*) 29 per cent., showing a considerable increase in the classes receiving the active liver product.

This seems to indicate that the administration of cod-liver oil might as well be dispensed with—a procedure which would doubtless bring joy to not a few disgusted sufferers—and in its place a more palatable fat be given, with pills or capsules of the extracted lecithides.

The Fundamental Value of Hepatic Extracts evidently depends—in a degree, at least—on the internal secretions present in these extracts, the administration of which supplements those of the disordered organ by introducing into the body the ready-prepared products of the normal liver, thus bringing to the hepatic cell units materials which stimulate their regeneration as well as their action.

Hepatic opotherapy, the value of which was first emphasized in 1896 by Gilbert and Carnot[4] of Paris, is based upon the fact that certain of the physiologic functions of the liver are transmitted in suitably prepared extracts of this organ, and that by administering preparations of this character one can demonstrate *in vivo*, as well as *in vitro*, several of the well-known physiologic powers of the liver. Their work has placed the application of liver preparations upon a scientific basis.

The therapeutic activity of liver extracts is not considered by all to be due to a certain specific substance or hormone. It is known that there are a number of ferments and heat-stable substances of a hormone nature in extract of liver, and it is likely that its curative value is due to a combination of all the active substances contained in the properly prepared extract.

Lorand[5] believes—and his opinions are corroborated by Gilbert, H. Strauss, and others—that the liver is a gland with an internal secretion that is strongly antagonistic to intestinal poisons, destroying toxic products brought to it from the intestine by the portal vein. This antitoxic power claimed for the liver is dependent, not upon the blood that may be present in the organ, but upon the liver tissue itself, and the activity of this organ in destroying toxins must be due to some chemical substance at present unknown. A part, at least, of this

power remains in vacuum-dried extracts, and is probably the source of the benefits which follow its therapeutic administration.

The Treatment of Digestive Disorders.—Naturally, then, the use of preparations of liver tissue has been tried in the treatment of digestive affections, and especially in constipation, for hepatic extract has a definite influence upon the functions of the liver itself, both as regards its presumed internal secretion as well as bile production.

For a number of years our French confrères have employed hepatic opotherapy with undoubted success. They have not contented themselves with the administration of several forms of bile and bile salts, but administer liver extract in various forms, principally in the form of cachets or tablets.

Stimulating Liver Inactivity.—The principal indication for this method of treatment is the presence of hepatic insufficiency. Unfortunately, there are numerous forms of this disorder, not a few of which are of a severe organic nature. Therefore we must not expect that any method of treatment consisting of the administration of any drug or drugs is going to regenerate a destroyed organ. We can, however, augment the diminished action of the partially destroyed organ by increasing the usefulness of the sound remainder, and thus render valuable service to the patient. Palliative treatment is better than no treatment.

In the strictly functional disorders of the liver surprisingly good results can be obtained, for hepatic opotherapy affords the overburdened organ an opportunity for self-regeneration. In hepatic insufficiencies associated frequently with a decrease of the solids in the urine, and especially in the amount of urea and other nitrogenous compounds, hepatic extract has served to good advantage.

Hepatic Cirrhosis.—This capacity of animal extracts to stimulate the function of the corresponding organ and—in a degree, at least—to favour regeneration has led to the use of hepatic extract in the treatment of cirrhosis of the liver. Experiences in the treatment of atrophic cirrhosis have been much more encouraging than in the hypertrophic form.

Spillmann and Demange[6] of Nancy have tested the applicability of this method, and have attempted to define its limitations. They have drawn the following conclusions from an extended experience: (1) Medication by means of liver extracts constitutes a rational and specific treatment for hepatic insufficiencies; (2) hepatic opotherapy has a decided action on nutrition, as well as an influence upon the urinary excretion; (3) the results following its use have been especially favourable in atrophic cirrhosis of the liver, passive congestion, and even cancer of the liver.

The following paragraph is quoted from their communication to the congress at Lille: "It is especially in atrophic cirrhosis of the liver that the effects of this form of opotherapy have proved favourable. In the first four cases we secured surprising results. In the first observation the general condition was so bad that we expected a fatal outcome. All methods of treatment had been employed without results. One month after commencing hepatic medication the patient was able to get up and follow the usual hospital régime."

The results following this method of treating atrophic cirrhosis are of a definite and tangible character. The amount of urine is increased from 100 to 300 per cent., and the urea index is markedly augmented. In addition to this, ascites is diminished, and in some cases entirely removed. Punctate hæmorrhage—a common complica-

tion—becomes less frequent, and finally disappears. In the terminal stages of cirrhosis, with cachexia and the inevitably rapid decline which usually terminates fatally, this form of medication is of no avail. It is idle, therefore, to attempt its use, or at least to expect results therefrom (for it is quite innocuous).

The Influence upon Hæmorrhage.—One of the first deductions made regarding the use of liver extracts was concerning their possible antihæmorrhagic influence. More than fifteen years ago, in an attempt to isolate an active principle from the liver, Mairet[7] prepared several substances which had an influence on the coagulation of the blood. Since petechiæ, hæmorrhage, and extravasation are not uncommonly found with disorders of the liver, it was inferred that these phenomena might be due to the loss of a certain element which was concerned in the coagulation of blood, and therefore in the prevention of hæmorrhage. The reasonableness of this theory was soon confirmed, and hepatic extracts are now used in the prevention and treatment of the hæmorrhages due to liver disorders as well as in disturbances of the blood-coagulating equilibrium, such as hæmophilia and purpura.

Gilbert and Carnot have used liver preparations in the treatment of hæmoptysis, especially in tuberculosis, with very encouraging results. Gilbert[8] was the first to emphasize the hæmostatic action of the liver extract in epistaxis and uterine hæmorrhages. Several writers have noticed, while using hepatic extract in the treatment of cirrhosis of the liver, that the oozing from hæmorrhoids, and also hæmaturic disorder, have abated.

Carnot,[9] in a paper on the therapy of the hæmorrhagic syndromes (read before the thirteenth Congrès Français de Médecine, 1912), reiterates his faith in hepatic opo-

therapy. His experience covers a large series of intractable hæmorrhages successfully treated in this manner after failure with other hæmostatic measures. In the treatment of the hæmorrhagic diathesis he called attention to the necessity for the use of organic extracts corresponding to the organic insufficiencies which may be present. If there is evident hepatic insufficiency, use liver extracts. In cases with evidence of renal disorder, with symptoms of uræmia, Carnot suggests renal extracts or the serum of the renal vein. In hæmophilia, however, he admits that hepatic opotherapy does not often give good results.

A Reported Action upon Phlebitis.—Another application of hepatic medication, of which the mode of action is somewhat obscure, has been mentioned by Keim.[10] He has tried the rectal administration of emulsions of fresh liver substance, both in the prophylactic and adjunct curative treatment of puerperal phlebitis. He suggests that in all cases the action of the intestines and liver must be supervised with special care during pregnancy, and the uterus should be completely emptied after delivery. Keim recommends the following somewhat empirical treatment, which, however, has given him gratifying results: 100 grammes of fresh calf's liver is thoroughly emulsified with 250 c.c. of water, and 10 grammes of peptone is added. This mixture is given as an enema. He regards this almost as a specific treatment, and has never had phlebitis develop in the cases in which the method has been applied, and records the prompt relief of symptoms in cases in which phlebitis had already developed. He states that Sobre-Casas has also reported equally favourable experiences with this form of opotherapy in puerperal phlebitis.

Possible Usefulness in Icterus.—Combe[11] of Lausanne

has used hepatic extract in the treatment of jaundice, and doubtless in some cases it may be helpful. In combination with bile it is likely to be considerably more effective (see Chapter XII.).

A Consideration of Hepatic Diabetes.—In diabetes, especially that form in which the pancreatic disturbance is a minor factor, and there are evidences of disturbed hepatic function—*diabète par anhépatie,* as the French term it—liver preparations have proved useful.

Personally, the author has come to the conclusion that the best method of arriving at any differential diagnosis is, in addition to the clinical diagnostic procedures, to administer suitable pancreatic preparations as a part of the regular treatment, and if no favourable result is obtained after one month (55 or 60 per cent. usually respond), to presume that the pancreatic causative element is absent or of minor consequence, and then to try the liver preparations.

On the other hand, it has been suggested that hepatic extract is deserving of a trial in all forms of diabetes, with the expectation that after a few days or a week the increase or decrease of the glycosuria will determine whether the treatment should be continued or not.

Now, the form of diabetes in which hepatic extracts are useful is associated with defective hepatic function, as a result of which this organ cannot retain the sugar ingested. The glycosuria in these cases is not very great, and seems to have a characteristic rhythm, appearing after the evening meal, then after all meals, and continuing with two maximum points—the one after lunch and the other after dinner. Occasionally the urinary sugar disappears entirely during the fasting period. At the same time, the amount of urea is particularly low—one-half the normal amount, or even less—while the

major symptoms of diabetes (thirst, polyuria, etc.) are not so marked. The tendency to infection and gangrene seems to be quite noticeable, indicating that the liver is failing also in its antibacterial powers.

Castaigne,[12] in a recent lecture, differentiates the several forms of diabetes, and urges the examination of individual specimens of urine passed at intervals of two hours. Glycosuria *post cibum* is quite likely due to disturbed hepatic conditions, especially if little or no sugar is found in the specimens passed remote from meals. The diagnosis is confirmed when the glycosuria is found to diminish or disappear after the administration of alkalies, hepatic extract, etc.

Such cases of diabetes do not usually culminate in coma. Acetone is not often found, and the usual signs of diabetes are not so patent. On the other hand, these cases are very liable to develop pulmonary tuberculosis, and Castaigne reports six out of sixteen cases of hepatic diabetes.

Labbé and Bouchage[13] consider glycosuria quite a common finding in the course of certain liver affections, and divide hepatic diabetes into five classes: (1) The glycosurias that occur during the course of hepatic lesions; (2) the hepatic congestions in overfed people; (3) the post-infectious or toxic hepatic disorders; (4) the *diabète sans dénutrition*, with enlarged liver of the overfed; (5) the hepato-pancreatic cirrhosis, with severe diabetes. They give a number of typical case reports to illustrate each of these conditions, and outline the treatment, which consists for the most part in mineral waters, hepatic opotherapy, and the lacto-vegetarian régime.

Gilbert and Carnot[14] have published numerous observations which demonstrate the value of hepatic prepara-

tions in those forms of diabetes which are associated with disorders of the liver. The dose is 30 to 60 grains (2 to 4 grammes), and it may be given three or four times a day.

Augmenting Elimination in Gout.—The capacity of liver extract to augment the detoxicating powers of the body has suggested a possible field of usefulness in gout and allied conditions. Some investigators believe that the ferments of the liver (preserved in carefully dried extracts) exert an influence on the metabolism of the nucleo-albumins, purins, and uric acid. Gilbert has noticed favourable results of this character, and advises the daily use of 30 to 60 grains (2 to 4 grammes) of desiccated liver extract in divided doses during the intervals between attacks. This adjunct, at present rarely used in England or America, seems to be none the less valuable, the more especially where the gout is accompanied by manifest hepatic indolence.

In Anæmia and Tuberculosis.—Attention has been called to the fact that the use of liver extract often is followed by a considerable increase in the red-cell count, and the suggestion has been made that this may be due either to a control of toxæmia or to an actual stimulating influence upon the hæmopoietic organs. The former theory seems the most reasonable, for it is well known that toxæmia, both alimentary and infective, is commonly found with anæmias, and that the toxic substances frequently manifest a hæmolytic influence. At all events, the use of this form of medication is of known value in toxæmias, and may often be associated with the orthodox treatment of anæmia with advantage.

Numerous other hepatic derangements, which are less serious and not associated with noticeable changes in the hepatic cell structure, especially the functional disturbances of digestion and nutrition, and particularly the

toxæmias and evidences of a waning of the normal detoxicating powers of the liver, often respond to this method of treatment. Several writers have emphasized the good results which follow the application of this idea in the treatment of certain infections, and particularly in tuberculosis.

Lereboullet places special emphasis on the important fact that the endocrinous organs suffer in a greater or lesser degree in tuberculosis, and that the alterations in function, and sometimes in structure, of these organs have a decided effect on the progress of this disease. "The logical conclusion, then, would be to resort to organotherapy to substitute or stimulate the function of these various organs." Here is Lereboullet's[15] opinion of the use of liver extracts in tuberculosis: "Most interesting is hepatic opotherapy, which, as a symptomatic medication in hæmoptysis, has given good results, and which has recently been praised by Triboulet in the tuberculosis of alcoholics with liver disease. Personally, I have several times seen favourable results in tuberculous alcoholics, especially where enlargement of the liver was present, and whether hæmoptysis was present or not." Liver medication is essentially an adjunct in tuberculosis, and its use should be limited to those in which the symptoms indicate that it may be useful.

The author has seen very encouraging results follow the use of a combination of extracts of liver, spleen, and pancreas,[16] the principal evidence of their value being the modification of nutrition and the augmentation of weight which followed several weeks of this adjunct treatment.

Parmentier[17] believes that hepatic extract exerts a favourable influence on the tuberculous. It increases weight, controls night sweats, and benefits hæmoptysis.

Gérard and Lemoine[18] have brought out a petroleum-ether extract of bile, called *paratoxine*, which they recommend in tuberculosis. Its action is not due to the active substances of liver extract, and is referred to in Chapter XII.

Combining Biliary and Hepatic Extracts.—According to Gilbert and Carnot, hepatic extract has a comparatively insignificant effect upon the bilogenic function of the liver. It cannot be used effectively in disorders of the biliary secretion. It will be found, however, that the activity of hepatic extract in this direction is considerably enhanced by combining with it a dried and purified extract of bile, and it will also be noticed that the action of bile preparations are increased by combining them with liver extracts. The two are complementary, and where both the general hepatic function and its bilogenic capacity are diminished, a bilo-hepatic extract will prove very useful. The author has used a combination similar to that just mentioned, with the addition of a secretin-bearing extract of the duodenum. It is a splendid combination for the treatment of chronic constipation and disorders of the liver.

Dosage and Administration.—In the application of hepatic medication it is necessary to use rather generous dosage, and little or no harm can result from it, as hepatic extracts are very slightly toxic (the toxic limit has been set at 60 grammes of liver substance per kilo of body weight), and cause no unfavourable reactions. The average dose of vacuum-dried liver extract (which corresponds to about 15 per cent. by weight of the fresh organ) is 15 to 20 grains (1 gramme), and 15 grains (1 gramme) can be given every two hours, and increased to as much as 60 grains (4 grammes), three or even four times a day. Liver extracts are obtainable in numerous forms for

administration by mouth—in dried or liquid form—or hypodermically.

The hypodermic and intravenous routes are not advisable, as toxic accidents have occasionally resulted, due to the introduction at one time of too great a quantity of the extract. This is obviated by giving the extract by mouth or rectum. Either mode of administration is effective, as the digestive juices have no appreciable influence upon these preparations, certain statements to the contrary notwithstanding.

As with other organic preparations, there seems to be no reason for discontinuing other treatment—*i.e.*, hepatic opotherapy is complementary to the indicated procedures. Hepatic organotherapy is a useful addition to everyday therapeutics, even though we will only admit that no other influence can be specifically attributed to the administration of the hepatic extract than the stimulation of the normal hepatic functions.

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CHAPTER XII

THE THERAPEUTICS OF BILE PREPARATIONS

Early References to Bile as a Medicine—The Broader Functions of Bile—Bile as a Cholagogue—The Indications for Bile Administration—Constipation—The Prevention of Hepatic Colic—The Pathogenesis of Gall-Stones—Increasing the Digestion of Fat—The Treatment of Muco-Membranous Colitis—Bile Extracts in Tuberculosis—Dosage and Administration.

WHILE the bile, as everyone knows, is produced by the liver, its action is quite different from that of liver extracts, and its administration must not be confounded with hepatic opotherapy. Strictly speaking, bile does not come within the scope of a volume of this character; so far as we know it does not contain a hormone, and the administration of bile derivatives is not hormone therapy, but it seems advisable, nevertheless, to follow a discussion of the administration of hepatic extracts with a brief outline of the possibilities of extracts made from bile.

Early References to Bile as a Medicine.—The use of bile in medicine dates back thousands of years. Nearly five hundred years before Christ, Hippocrates prescribed oxgall and honey in the form of suppositories for congestion of the bowels. It is recorded that Dioscorides, in B.C. 75, treated a number of digestive disorders with the bile of hedgehogs, and from those remote days to the present, occasional references have been made to the esteem in which gall was held as a therapeutic agent.

It will not be necessary here to go into the physiology

or chemical composition of bile secretion. One fact is to be emphasized: certain of the biliary constituents, after serving their purpose in the intestinal canal, are reabsorbed into the blood, thus returning to the liver and bringing about its bile-producing function. This fact is generally appreciated, and for this reason bile is regarded as the best of the cholagogues and numerous preparations of bile are now in general use. Notwithstanding its value, the mineral and vegetable hepatic stimulants are still much more extensively used.

The Broader Functions of Bile.—It happens that the possibilities of what has been called " biliary opotherapy " are considerably broader than its cholagogue action, and a number of new facts have been recently discovered regarding the rôle of bile action in the intestine.

Roger,[1] who is an authority on this subject, gives a concise résumé of this subject, and summarizes his conclusions under the following seven propositions:

1. The bile does not contain digestive ferments, but exercises a strengthening influence on other enzymes, augmenting the action of certain ferments, such as pancreatic amylase and intestinal lactase.

2. It has the property of abstracting from the intestinal walls those ferments which have been elaborated therein, notably invertase, and therefore plays an important part in the digestion of certain forms of sugar.

3. It is concerned in the digestion and absorption of fats.

4. It exerts a special action on albumins and peptones, which it precipitates from the acid solution in order to redissolve them immediately.

5. Bile has no bactericidal properties, but it hinders intestinal putrefaction in three ways: (1) By favouring the development of certain micro-organisms, such as the

colon bacillus, to the detriment of the anaërobes, which are the principal elements in the causation of putrefaction; (2) by diminishing the secretion of ferments by bacterial flora; (3) by exerting a hindering action upon the influence of the bacterial ferments on fermentable matter.

6. It diminishes the toxic action of the product of the intestinal flora.

7. It prevents the coagulation of mucus in the intestine by the so-called "mucinase" (which asserts itself under the disordered conditions due to lack of bile); the deficiency or absence of the biliary secretion explains the genesis of certain forms of muco-membranous enteritis.

Bile as a Cholagogue.—We are told by the French clinician, Huchard, that "bile is the physiologic cholagogue, just as urea is the physiologic diuretic," and by far the most important therapeutic service that the administration of bile or its preparations can render is its bile-inducing action.

Bile gives very good results in those cases where the biliary secretion has been totally or incompletely arrested, as in icterus and hepatic colic, as well as in the other more common disorders where the biliary secretion is insufficient.

Its use prompts a more normal condition in the intestine, and favourably controls certain forms of constipation, bringing about its salutary action by several methods which have already been enumerated. Some experiments by Dauguet[2] give weight to the importance of bile as a cholagogue. He found that if 100 c.c. of bile (containing 1·53 grammes of the biliary salts) is introduced into the stomach, a secretion of bile is brought about with a total of 4·53 grammes of bile salt, whereas before the experiment this amounted only to 1·86 grammes.

Clinically the results are just as good. The report of

Delore and Cotte[3] upon the results of the administration of *cholêine* (an extract of ox-gall) to an individual with a biliary fistula is of special interest, as it shows how great is the quantitative influence of this form of medication. Before the test the amount of bile collected from the tube varied from 103 to 200 c.c. The exhibition of 0·6 gramme (approximately 10 grains) of the extract raised the excretion of bile to 550 c.c., and 1·2 gramme (20 grains) still further increased it to 750 c.c.

The Indications for Bile Administration.—The principal disorders in which the administration of bile is indicated are hepatic and biliary insufficiency with constipation, fermentation in the bowel, auto-intoxication, hepatic colic, biliary lithiasis, and other forms of occlusion of the ductus choledochus (including the inflammatory conditions), and muco-membranous enterocolitis. We will briefly consider each of these separately.

Constipation.—More than 50 per cent. (some authorities say as high as 90 per cent.) of all cases of constipation are due to disorders of the liver. The liver becomes " torpid " from overwork and long abuse, and needs the right kind of stimulation. Bile is the remedy *par excellence*, because it is the best cholagogue, and also because it is actually the missing element. It must not be thought, however, that one can do more than begin to replace the reduced quantity of bile in the intestine, for the normal average flow of bile is 1,200 to 1,300 c.c. in twenty-four hours, 15 per cent. of which (or 180 to 200 grammes) consists of solid elements; and of course even half that amount of inspissated bile would be a most inconvenient dose.*

The results of this form of treatment are less strenuous

* Although Dauguet has shown that a dog of average size can take 300 grammes of ox-gall (representing about 45 grammes of solid elements) with no toxic phenomena and only a rather severe diarrhœa.

than the usual cathartics, and it has the advantage of being a rational restorative procedure rather than a vigorous whipping, as with calomel. As a matter of fact, 10 grains of bile extract are usually cathartic, and 3 to 5 grains (or more) continued for some weeks form a most satisfactory treatment of chronic constipation, the fœtid odour of the stools being rapidly controlled, their consistency and regularity being brought to normal, and with these changes there is naturally a regulation of the toxic manifestations, the colour of the skin, and the health in general.

It is unnecessary to repeat the observations of Roger and others on the value of bile as an intestinal antiseptic. While not antiseptic itself, bile is one of the best intestinal antiseptics, because it facilitates the re-establishment of the normal conditions in the intestines.

The Prevention of Hepatic Colic.—Tradition has set apart ox-gall as a marvellous remedy for colic of hepatic origin, and during the past twenty-five years this empirical confidence has been justified by our knowledge of how and in what degree the bile acts.

Manifestly one cannot expect any preparation of bile to control the pain or inconvenience of hepatic colic. The acute manifestations must be controlled in the usual manner by heat and opiates; but nevertheless bile is a most reasonable *curative* remedy, because it tends to obviate the stagnation and thereby to facilitate the removal of concretions obstructing the bile channels.

So far as we know there is no remedy that will dissolve gall-stones *in situ*, and bile is no exception to the rule, nor will it facilitate the passage of a stone too large for the duct. Its augmentation of the flow of bile may favour the removal of the obstruction provided it is not solidly fixed, in which event the only recourse is to surgery.

The Pathogenesis of Gall-Stones.—The importance of normal bile production is even greater than has just been indicated, for Chauffard[4]* and his assistants have demonstrated that when there is a reduced supply of bile salts, the cholesterin (which it will be remembered is the chief consistent of gall-stones) is not held properly in solution, and hence is retained in the blood. This excess facilitates precipitation at points favourable to sedimentation, especially in the gall-bladder and ducts. The principal disorder is a form of hepatic insufficiency, and an attempt should be made to restore the normal activity or to supplement it by administering bile and liver preparations, in addition to the usual hygienic and dietetic measures.

Increasing the Digestion of Fat.—Bile is an important factor in the digestion of fats, and without going into the physiology of this occurrence we may say that the administration of bile regulates, in a considerable degree, further absorption. Carnot[5] has shown that extracts of bile favour an increase in weight, since by their influence the assimilation of fat may be increased as much as 75 per cent. Robin states that fully 95 per cent. of ingested fats are metabolized, but if the proportion of bile decreases, one-half of the fat is not assimilated.

The therapeutic indication of cream-coloured stools is almost invariably bile.

The Treatment of Muco-Membranous Colitis.—To the French is due the credit for having enlightened us upon the pathogenesis of muco-membranous enterocolitis, and thereby upon an effective treatment for it. The researches of Roger[6] on the coagulation of mucus in the intestines, and the regulative action that the bile exerts upon this

* Chauffard has just published a new book (see Appendix) which considers the whole subject of biliary lithiasis. Chapters I. and X. especially concern the pathogenesis and treatment of this condition.

phenomenon, have demonstrated a close relationship between intestinal affections, especially mucous enteritis and colitis, and the normal supply of bile.

It seems that the intestinal walls normally secrete a ferment named by Roger "mucinase," the function of which is to coagulate mucin. This ferment is rendered inactive by certain alcohol-soluble, heat stable substances in the bile, and Roger inferred that, since this disease was so often associated with biliary insufficiency, and experimentally produced by diverting the bile-flow from the duodenum, the membrane formation was due to insufficiency of bile. Later Riva isolated mucinase in the fæces of patients suffering from this disease. From these studies we have come to recognize the value of bile as a remedy for this intractable and painful disease.

Nepper[7] and others have also investigated the subject very carefully, and supplemented their physiologic investigations with a large number of clinical tests. He puts forward as an axiom that muco-membranous colitis is the result of deficient bile production (*oligocholie*), and cannot exist without it, and also that the membrane is due (1) to the increase in the ferment mucinase, and (2) to a relative and simultaneous diminution in biliary secretion, especially as regards its anticoagulating power, which permits the mucinase secreted by the epithelial walls of the intestine to assert its coagulating powers.

This explains the following statement in Roger's book on digestion[8]: "For those who pass membranes, prescribe an extract of ox-gall, and you will frequently see a subsidence of the pain and a complete disappearance of the membranous casts."

This disease may be treated locally or by oral administration of bile. Nepper administers solutions of bile by means of high rectal injections, allowing the solution to

remain in contact with the membrane-covered intestinal walls for about two hours, carrying out a procedure exactly similar to the orthodox high rectal injection. He also supplements this by a course of pills containing bile extract, which should be preferably keratin coated. The dose by mouth varies from 5 to 20 grains, and may be given at intervals of two or three hours. It seems advisable to continue the administration of bile in slightly smaller doses for some months after the colitis is controlled.

Bile Extracts in Tuberculosis.—Lemoine and Gérard[9] seem to have established the value of a petroleum-ether extract of bile (*paratoxine*) in the treatment of tuberculosis. It must be admitted, however, without in the least degree depreciating the results obtained, that the extract is virtually a solution of cholesterin, and its virtues are due to the power of this lipoid to "fix" certain toxic substances.

It does not seem, then, that the subject rightly comes under the title of this chapter, but it will be briefly referred to again in the chapter devoted to the lipoids.

Dosage and Administration.—The average dose of extract of bile is 8 to 25 grains (0·5 to 1·5 grammes) from two to five times a day, or of the repurified and vacuum-dried preparation 5 to 10 grains (0·3 to 0·6 gramme). The French preparations are usually put up in keratin-coated pills or ovoids, each containing 0·2 gramme (3 grains) of the extract.

In constipation small doses over a long period are advised, and extracts of liver and duodenum may be combined with bile to considerable advantage (see p. 168). In hepatic colic it should be given in frequently repeated doses (3 grains every hour during attacks), and should be kept up during the intervals in 6-grain doses four or five times a day. The dosage in colitis has already been suggested.

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CHAPTER XIII

THE THYROID GLAND AND THE TREATMENT OF ITS INSUFFICIENCIES

The Keystone of the Endocrinous System—The Thyroid Hormones—The Polyvalence of the Thyroid Secretion—The Influence of the Thyroid on Nutrition—The Relation of the Thyroid to the other Ductless Glands—The Iodine in the Thyroid and Extracts thereof—The Rise of Thyroid Therapy—The Artificial Replacement of the Thyroid Secretion in Myxœdema, Goitre, etc.—The Frequency of Functional Hypothyroidism—Levi and de Rothschild's Deductions—The Basis of Empirical Thyroid Therapy—The Treatment of Obesity—Immunity, Resistance, and Detoxication—Thyroid Therapy in Rheumatism—The Value of Thyroid Extract in Dermatology—The Use of Thyroid Extract in Gynæcology—The Action upon the Vascular System—Nervous Disorders and their Treatment with Thyroid Extract—Nutrition and Developmental Disorders in Children—The Newer Conceptions of Graves's Disease—Pluriglandular Combinations—The Contra-indications to Thyroid Therapy—The Indiscriminate Use of Thyroid Preparations—Dosage of Thyroid Preparations.

THE literature on the thyroid gland and its internal secretion, as well as on the therapy which this knowledge has made possible, is immense. Many hundreds of papers have appeared since the inauguration of this most important study. Not a few books are devoted solely to this subject, and if all the information at present on record could be gathered here, it would add many hundreds of pages to this book.

Thyroid therapy is the best known application of hormone-bearing products in therapeutics, and its value

in certain conditions makes it possible to class it with that limited number of remedies known as "specifics."

Here it is only possible briefly to summarize the gist of our knowledge, and perhaps to emphasize the fact that thyroid therapy has a considerably broader field than is generally known, and that its value is by no means limited to the control of those glandular insufficiencies which are obvious, and which might properly be called "major thyroid insufficiencies."

The Keystone of the Endocrinous System.—The thyroid has been called "the keystone of the endocrinous system," and the use of preparations of it is virtually the foundation-stone of modern organotherapy. It is really amazing how our knowledge of its usefulness has developed in little more than two short decades.

The views concerning the function of the thyroid have been frequently changed, and have varied from the presumption that it was a comparatively useless fatty covering of the neck, to the more scientific suggestion that it acted as a regulator of the hæmopoietic and circulatory mechanism. Galen knew of its existence, and even described it as a ductless gland, but offered no suggestions regarding its action. The early views of the function of the thyroid are summarized in a very interesting manner in Swale Vincent's book.[1]

The Thyroid Hormones.—This remarkable gland produces and discharges into the blood and lymph a complex secretion, which contains the active principle or hormone. This substance influences certain tissues directly, and by its profound action upon metabolism indirectly affects many functions of various organs. For a long time the mode of these activities was not well known, and within the present decade the thyroid secretion is referred to as acting "probably through the nervous system." There

can be no doubt that it acts *on* the nervous system, but it seems conclusively proved that it acts through humoral channels, and physiologists generally credit the thyroid action to its hormone-content.

Schäfer, in his address,[2] refers to the important position of the thyroid in the following terms: " Another instance of an internally secreting gland which is essential to life—or, at least, to its maintenance in a normal condition—is the thyroid. The association of imperfect development or disease of the thyroid with disorders of nutrition and inactivity of the nervous system is well ascertained. The form of idiocy known as ' cretinism,' and the affection termed ' myxœdema,' are both associated with deficiency of its secretion. Somewhat similar conditions to these are produced by the surgical removal of the gland. The symptoms are alleviated or cured by the administration of its juice. On the other hand, enlargement of the thyroid, accompanied by increase of its secretion, produces symptoms of nervous excitation, and similar symptoms are caused by excessive administration of the glandular substance by the mouth. From these observations it is inferred that the juice contains hormones which help to regulate the nutrition of the body and serve to stimulate the nervous system, to the performance of the higher functions of which they appear to be essential. To quote M. Gley, to whose researches we owe much of our knowledge regarding the functions of this organ: ' *La genèse et l'exercice des plus hautes facultés de l'homme sont conditionnés par l'action purement chimique d'un produit de sécrétion. Que les psychologues méditent ces faits !*' "

The Polyvalency of the Thyroid Secretion.—The chief means of studying the action of this gland has consisted in the clinical consideration of the several disorders of

the thyroid. The variability of these symptoms has led Murray,[3] amongst others, to the belief that the thyroid secretion is polyvalent, and contains different hormones which are capable of activating different organs. This rather suggests that one of these hormones may have a special influence upon the sweat glands and hair follicles, while another may influence the heart, still another the bronchial mucous membrane, and so on. Attention is called to the fact that in some cases of Graves's disease not only may there possibly be an increase in the amount of thyroid secretion, but in some cases also a considerable difference in the proportion of the hormone-content of the secretion. Sudden temporary increases in various of these hormones would account, for example, for the so-called "goitre heart." This theory is sufficiently inviting to build upon it the idea that the various forms of hyperthyroidism are due to variations in the characteristics of the increased thyroid secretion that is absorbed. Further proof of the polyvalent character of the thyroid secretion will be found in the consideration of the influence of thyroid extract upon the heart and blood-pressure. This may also account for the very extended list of indications for thyroid therapy, and especially for the large class of widely varying conditions which are presumed to be due to functional hypothyroidism.

Siegmund[4] is convinced of the soundness of this theory, and relates experiences to show that from the standpoint of the therapeutic activity of thyroid preparations (as compared with the varying symptoms of thyroid excess) in certain cases Baumann's *iodothyrin* failed, while ordinary thyroid extract was very effective, and *vice versa*. He concludes that there are numerous substances produced by the thyroid gland, the absence or diminution of which may explain the simultaneous occurrence of thyroid

weakness and thyroid hypersecretion, and their consequences. Each of these substances probably has a definite function and a special relation with a definite tissue or organ, including the other endocrinous glands.

The Influence of the Thyroid on Nutrition.—While a number of the ductless glands are intimately concerned in the regulation and maintenance of nutrition, none of them play such a decided part as the thyroid. It may be said that the thyroid presides over the nutrition of the body, although, of course, its influence is augmented from many other quarters. It is difficult to set down within these brief limits an adequate discussion of the importance of this subject, for it is peculiarly complex.

The extraordinarily stunted condition of cretins, the prevalence of disordered fat metabolism in patients suffering from comparatively slight thyroid insufficiencies, the relation of thyroid disease to bone growth, and, finally, its intimate connection with the establishment of the sexual activities and the accompanying mental and physical growth, are all incontestable evidences of the essential influence of the thyroid on metabolism and nutrition.

The major share of this control of growth and the bodily interchanges generally is undoubtedly purely thyroid in origin, and while obvious connections may be traced between other internal secretory organs and various phases of nutrition, it will be astonishing how closely the thyroid is concerned in the work of these other glands.

The Relation of the Thyroid to the other Ductless Glands.—The importance of the interrelation between the thyroid and its endocrinous fellows has already been considered (Chapter III.), and it is well known that the evidences of these relations are more thoroughly worked

out than is the case with any of the other endocrinous glands. As we have seen, the thyroid is in known and proved relations with the adrenals, pancreas, hypophysis, and gonads, and very probably quite intimately connected with the thymus, parathyroids, and intestine. A still more indirect relation may be traced between the thyroid and the remaining members of the endocrinous family. A knowledge of these relations is of paramount importance in the consideration of all metabolic disturbances, as well as in disorders of any of the above-mentioned organs; in fact, the thyroid should be taken into consideration in the study of practically every phase of internal medicine. There is nothing speculative in the greater part of the information which we now have at our command, though much of this definite knowledge was admittedly quite speculative a very few years ago.*

Briefly, then, it may be well to recapitulate the principal relations between the thyroid and the other important ductless glands, since upon this knowledge depends the effective and successful basis of thyroid therapy. Evidence has been collated by Hoskins[5] to show the interrelations of the endosecretory organs. The thyroid by its internal secretion stimulates the adrenals. Its relation to the hypophysis may be called that of a mutual friend, and it has been presumed, as a result of a number of experiments, that the hypophysis under certain circumstances functionates vicariously for the thyroid. This, however does not preclude the idea that the thyroid normally exercises an inhibitory action upon the hypophysis, as indicated by the pituitary hypertrophy which,

* This should be of considerable encouragement to us in our consideration of the less well-known endocrinous organs, for undoubtedly knowledge concerning them is destined before very long to be put upon a much more definite basis.

so constantly seen, is associated with experimental or clinical athyroidia.

The influence of the thyroid upon the testes and ovaries is of such a nature that it is now stated definitely that the thyroid controls the activities of these glands, and furnishes at least the major part of the stimulating effect that is necessary for the normal continuance of their functions.

Hertoghe[5a] has shown that the thyroid secretion is indispensable to the establishment of the activities of the gonads. He was also the first to point out the antagonistic action which the thyroid exerts upon the ovarian secretions. Attention may also be called to the fact that the thyroid evidently exerts an action upon the menses, for myxœdematous females frequently suffer from profuse menstrual hæmorrhage which is not easily controlled, while thyroid medication moderates it in a remarkable manner. On the other hand, women with Graves's disease frequently have a diminished monthly flow which even may amount to complete amenorrhœa.

The thyroid also influences the mammary secretion. Hertoghe reports that the administration of thyroid extract to lactating animals augments, in a considerable degree, the amount of milk produced.

Reference has already been made to von Noorden's ideas regarding the antagonistic interaction of the thyroid and pancreas (Chapters III. and VII.).

The evidence regarding the relation of the thymus to the thyroid is somewhat conflicting. The experimental work indicates that there is a connection between these organs, but whether it is a synergism or an antagonism is not quite clear, as under certain experimental conditions both these stimuli may be brought into play.

It is, of course, understood that these relations just

mentioned are subject to numerous stimuli from other sources, and while quite definite statements are now generally made, it is very easy, in both experimental work and clinical observation, to bring forward presumable evidence to show how much we are still in the dark about what we consider to be the best-known facts regarding the correlation of the thyroid with the other ductless glands.

The Iodine in the Thyroid and Extracts thereof.—The thyroid gland is very rich in iodine, containing as it does nearly ten times more of this element per gramme of gland substance than any other organ or tissue. This iodine is considered to be the active element in the thyroid secretion, since it has been shown that the therapeutic activity of thyroid preparations varies directly with their iodine content; in fact, the importance of the presence of iodine in thyroid extract has established the iodine percentage as the recognized standard of efficiency of such extracts. The essential rôle of the iodine is emphasized by Osborne,[6] who remarks at the close of a valuable paper that, "though much of the thyroid substance on the market is not active, a little coincidentally administered iodine as an iodide will render it active." This, however, should not permit of the use of any but the most active products obtainable.

It now seems to be evident that many of the failures of thyroid therapy, and of the varying results that were so commonly found some years ago, were due to the uncertain iodine content of the preparations. Fortunately we have passed this stage, and practically all trade preparations are now standardized to contain 0·2 per cent. of actual iodine.

It must not be imagined that the iodine is the active principle, for in spite of the important part that this

element plays in the presumed molecular make-up of the thyroid hormone, it cannot be used as a substitute.* The combination is as yet too complex for the biological chemist; but it is predicted that before long a graphic formula will have been worked out, just as has the formula of *adrenalin*, and iodine will be found to be an important part of it. In all probability a synthetic product resembling thyroid extract eventually will be produced, just as *suprarenin* is now made in the laboratory with no recourse whatever to animal mother-substances.

The Rise of Thyroid Therapy.—As soon as Schiff and Horsley (1884-86) showed that the thyroid was essential to the well-being of the body, the study of its influence in health and disease was taken up with avidity. The innumerable experiments on animals and clinical researches in medicine, which were thus initiated, opened up a field of physiology that had been hitherto unseen; and as a better knowledge of the activities of the thyroid was gained, it was but a step to apply the fundamental rule of organotherapy, and to attempt to use thyroids, raw or extracted, in the treatment of the deficiencies of this organ. The results, as all know, were startling; and upon these experiences, in a far greater degree than upon the experience of Brown-Séquard with testicular extract, the scientific and rational foundation of hormone therapy has been laid.

The credit for having first applied thyroid preparations in clinical practice must be awarded to G. R. Murray[7]

* Swale Vincent, in his book (p. 352), is not quite so emphatic. He writes: "As to the chemical nature of the internal secretion, nothing definite is known. The significance of iodine is problematic, though the beneficial effects of thyroid substance administered as a drug seem to depend very largely upon its iodine content. It is impossible altogether to escape from the suspicion that treatment with thyroid preparations may after all only be a mode of treatment with organically combined iodine in an easily assimilable form." The present author, like many others, does not quite agree with this.

of England. Gley,[8] in France, and Vassale,[9] in Italy, were then at work with the initial attempts to control the disorders produced by thyroidectomy in dogs.[7a] In 1890-91 these investigators independently published the beginnings of the voluminous literature on thyroid medication. The comparatively crude preparations then used have passed through a process of evolution, until to-day the profession is served with numerous active and standardized products,* and has a very much more thorough idea of their therapeutic indications and clinical possibilities. But the maze of thyroid action and interaction is so complex, and the range of the limitations of thyroid therapy so great, that there are yet many points to be learned. Only a short time ago (1914) the author learned, in a personal communication from Beebe, that he had isolated a new and hitherto unknown "X-substance" from the thyroid, which has a marked hypotensive action, without the therapeutic effect usually expected from thyroid preparations. Further reference to this will be made later.

The Artificial Replacement of the Thyroid Secretion in Myxœdema, Goitre, etc.—This is not the place to discuss the relation of the thyroid to simple goitre, myxœdema, endemic or sporadic cretinism, or cachexia strumipriva. This is well done in several books and "systems" of medicine; but it is necessary briefly to mention the salient facts involved, in order that the chief link in the chain of thyroid therapy may not be omitted.

It is now an unquestioned fact—and unquestioned facts in medicine, especially in therapeutics, are very few and far between—that hypothyroidia and athyroidia are amenable to treatment with thyroid extracts. The

* In an annotation accompanying the MSS. of this chapter Professor Murray remarks: "It is curious that my original thyroid extract is still to-day the official B.P. *Liq. thyroidei*."

literature is as extended as it is convincing, and thyroid extract is conceded to be numbered among the very few "specifics." It is the cure* for myxœdema and athyroidia.

The Frequency of Functional Hypothyroidism. — In goitre the thyroid may be inactive, underactive, or overactive. Individuals with an inactive thyroid are virtually suffering from myxœdema, and exhibit a series of symptoms diametrically opposed to those of patients with an overactive thyroid. When the thyroid is underactive, the results of its deficient supply of hormones may or may not be manifested. A marked hypothyroidism is akin to, and may be called, "myxœdema." More often, however, this faultiness is not so evident, and in such cases we have the minor form of thyroid incompetence, which Hertoghe has called "*myxœdème fruste.*" He was the first to lend emphasis to the so-called "benign thyroid insufficiencies." In 1899 Hertoghe[10] introduced the term "*hypothyroïdie benigne chronique,*" and the study of this subject rapidly became popular in Europe, and especially in France was investigated by numerous authors, including Leopold Levi, de Rothschild, Delacour, Apert, Trémolières, and others, who warmly defended this position. The subject is fully considered in the report of Verriest,[10a] who was selected to analyze Hertoghe's work on the lesser forms of myxœdema, and report upon it to the Belgian Academy of Medicine. A knowledge of this minor and frequently overlooked thyroid inadequacy is of considerable therapeutic service, as we may shortly see.

* By "cure" is meant "a medicine effective in treating disease" (Dorland). Of course, the thyroid treatment does not grow a new gland in the congenitally athyroidic, nor does it regenerate a hopelessly atrophied gland; but it does relieve and remove the symptoms, and in a degree the stigmata, of this condition, keeping them in control as long as the remedy is judiciously administered.

If the major thyroid insufficiencies be termed " phases of organic hypothyroidism " (for in them all there is an obvious change in the thyroid structure), then it is right to assume that there must be a corresponding functional disturbance in which the secretory activities of the gland are modified with no evident change in the structure. This disorder has also been called " chronic benign thyroid insufficiency," or Hertoghe's syndrome. This is undoubtedly a clinical entity, and it may be connected with a large variety of endocrinous syndromes, as well as with many conditions not yet definitely connected with disorders of the internal secretory mechanism. Many obscure conditions are undoubtedly associated with, and in many cases probably due to, minor thyroid insufficiency—a condition for which the author suggests the term " functional hypothyroidism."

Levi and de Rothschild's Deductions.—Since Hertoghe originated the study of this subject, Leopold Levi and Baron H. de Rothschild, of Paris, have been among its foremost students, and an hour or two with their latest book* will convince the most confirmed sceptic that what Leonard Williams has said of thyroid therapy is very true: " The broad lines of thyroid therapy are simple enough, but the byways are fascinatingly complex."

A few points culled from the introduction to this book

* " La Petite Insuffisance Thyroïdienne." It has been said that the writers of this book are " thyroid mad," and that every case they mention is related in some way to a disorder of the thyroid. This may be quite true, but it should be remembered that MM. Levi and de Rothschild are studying the intricacies of known and supposed *thyroid disorders*, and purposely look at the subject from this particular view-point. They may not be invariably right in their deductions, nor may the clinical tests of their suggestions be always successful; but it is quite certain that the physician who acquaints himself with the observations of these gentlemen, taking as much of the proverbial "grain of salt" as may seem to be necessary, will find his appreciation of hormone action and thyroid therapy broadened in a degree which the author is convinced will be of much practical help.

will explain how and why these authors draw their conclusions: "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.

"In 1905 we first tried thyroid therapy in conditions other than myxœdema. The first subject suffered from chronic rheumatism and psoriasis. After commencing this medication, the appetite was increased to a point where it seemed that the patient might have a tapeworm; and the patient also was remarkably relieved of extreme sensitiveness to cold. This directed attention to the influence of the thyroid upon the appetite and bodily warmth. Later a favourable action upon constipation was noticed, and the similarity was remarked between these symptoms and those of myxœdema, the difference being merely one of degree.

"We then encountered a case of severe constitutional neurasthenia in a girl showing numerous signs of hypothyroidism—*e.g.*, short stature, anorexia, sensitiveness to cold, loss of hair and teeth, cracking noises in the joints, a tendency to colds, a bad state of the gums, hæmorrhoids, etc. Were these phenomena and the neurasthenia coincidental with, or actually due to, the hypothyroidism? The treatment was effective, and after taking sixty-one cachets (each containing 0·1 gramme—1½ grains—of thyroid powder) the patient considered herself cured. Two months later there was a relapse, which, however, was again controlled in the same way. This therapeutic experience indicates a relation between hypothyroidism and certain forms of neurasthenia.

"In the same manner we have studied transitory œdemas, periodic herpetic anginas, nervousness (especially in children), neuroarthritic disturbances, migraine, asthma, certain dermatoses, etc. When thyroid therapy controls these diverse symptoms, one must admit that hypothyroidism, in a certain degree, was concerned in their production. Hence the treatment itself acquires a diagnostic value."

The Basis of Empirical Thyroid Therapy.—These investigators wisely warn against a common source of error, which must be avoided if our deductions are to be of value. For example, hypothyroidism is an extremely common condition; adenoids, incontinence of urine, and rickets are far from rare. Have we, then, the right, when in some subject we meet evidence of hypothyroidism and adenoids, to conclude that there is a thyroid origin of the adenoids? Another example, chronic rheumatism, is often of thyroid origin. Now, it may coincide with myxœdema without being influenced by the thyroid treatment. The application of this treatment offers no irrefutable proof one way or the other. Clinical medicine merely permits us to suppose a thyroid origin for this phenomena or that, it cannot prove it absolutely. Even in myxœdema the symptoms may not all necessarily be due to the deficient thyroid secretion, for other local troubles may, and often do, intervene to produce certain of the symptoms. Hence clinical experiences do not permit definite conclusions, but simply lead to the utilization of a method of treatment.

This, then, is the *raison d'être* of the empirical use of thyroid extract—an immensely valuable procedure which is "quite unscientific," but none the less resultful. This is by no means an isolated experience, for there are a large number of established therapeutic measures in general

use for which, on the closest analysis, one cannot assign a fundamentally scientific excuse.

The mode of action of the thyroid hormone is not known, at least in detail. It is not likely that its influence is confined to the thyroid itself: its stimulating powers may reach the whole endocrinous system. Hence there is a likelihood that thyroid medication not only re-establishes the thyroid equilibrium, but also tends to restore the internal secretory balance. This may account for the remarkable action of thyroid medication in some conditions, as well as for the activating effect of minute doses of thyroid extract upon other glandular substances given simultaneously (see Chapter XXX.).

The Treatment of Obesity. — One of the empirical applications of thyroid therapy that is most frequently made is in the treatment of obesity. There is no doubt that many of the individuals with this disorder, especially women, are in a state of hypoendocrinism, and that the judicious use of thyroid may stimulate the metabolism and enhance oxidation, thus reducing a part of the superfluous fat. Just how this is accomplished is difficult to say, but the treatment has come into quite general use, in spite of some drawbacks which must be briefly referred to. The use of organotherapy in "home medicine" is not advisable. Always it is best to have patients who are undergoing treatment, whether with thyroid, ovary, adrenal, or pituitary preparations, under close professional observation. Thyroid extract is too often used in a senseless and indiscriminate manner, and in no condition does this obtain to such a degree as in obesity. As a result, not a little harm has been brought about, and conditions which are much more serious than obesity have resulted.

The dosage cannot definitely be stated, for too many

concomitant circumstances enter into the question. It is certain, however, that heretofore the doses of thyroid extract, especially in the treatment of obesity, have been far too large.

Immunity, Resistance, and Detoxication.—There can be little doubt that one of the most essential of the activities of the thyroid gland is concerned in the resistance of the organism to disease, and that the thyroid hormone is intimately connected with these factors which produce immunity. This appears to have been first suggested by Sajous[11] in 1903, and has since been confirmed by numerous clinicians and experimentalists. Sajous's original observations are interesting: "(1) The thyroid secretion is an active factor in the immunizing processes. (2) It takes part indirectly in this process by increasing the functional activity of the adrenals as well as general oxidation and metabolism. (3) The resulting increase of functional activity of the organs producing protective substances (alexins) correspondingly augments the quantity of these alexins in the blood.

Langmead[12] has considered the evidence which seems to point to a relationship between the thyroid gland and alimentary toxæmia. He believes that facts are accumulating to show that among the many functions of the thyroid one of the most important is a protective action against toxins which may enter the circulation. A series of cases is described by Langmead, in which dilatation of the colon produced symptoms similar to those of gastric tetany, and he calls attention to the reports of Sir Arbuthnot Lane and others, of the fact that the Lane operation —ileo-sigmoidostomy—was followed by a visible reduction in the size of the goitre.

Slosse[13] of Brussels has suggested that the disturbances in protein metabolism, which are commonly associated

with chronic joint diseases, especially in those cases in which the function is not of a gouty nature, and in which the metabolism of nucleins does not appear to be influenced, are probably related to thyroid inefficiency. According to his suggestion, we are to believe that the thyroid produces a deaminizing hormone, which specifically influences the course of protein metabolism. He remarked that when thyroid preparations were first given to sufferers from chronic arthritis of the type above mentioned, there was always an increase in the ammonium salts in the urine.

Thyroid Therapy in Rheumatism. — This detoxicating influence, with the hypothetical deaminizing hormone to which Slosse refers, may be the explanation for the frequent good results which follow the use of thyroid extract in the treatment of chronic rheumatic disorders. Numerous writers have called attention to the beneficial results in joint disturbances which are often associated with thyroid medication, and presumably are a result of it. Pathological evidence of thyroid disorder in chronic articular affections and in rheumatism has been brought forward by Aubertin and Pascarno,[14] who relate the autopsy findings in a number of cases in which well-marked thyroid lesions were prominent.

The *New York Medical Journal* in an editorial article discusses in the following terms the relation of the thyroid gland to chronic rheumatism[15]: "There is a form of rheumatism, not infrequently met with, which is distinctly due to hypothyroidism and associated with the characteristic symptoms of this condition; it consists of severe pain in the occipital region or between the shoulder blades, which rest in bed tends to aggravate rather than mprove. Such cases never yield to salicylates and other agents used commonly in the various forms of rheumatism;

but the patients gradually recover under the persistent use of desiccated thyroid gland. Care must be taken, however, to avoid large doses. The so-called 'average dose' of the United States pharmacopœia is positively dangerous here: in no case should the initial dose of desiccated gland exceed 1 grain."

Undoubtedly much of the good which follows the empirical use of thyroid extract is due to the enhancement of detoxication, and the stimulation of resistance which it indirectly brings about. Sajous,[11] in considering the antitoxic functions of the thyroid, aptly remarks that the recognition of the connection of the thyroid—always including the parathyroids—with the defensive mechanism of the body, enables us also to get better results in the treatment of goitre by emphasizing the importance of endogenous intoxication in the causation of the disease. A patient may not do well, as is often the case, under iodine or thyroid gland—or both combined, the best plan—even when given early, avoiding strictly all cases showing signs of Graves's disease; but this will soon change if, besides giving these agents, attention is paid to any condition whatsoever—intestinal, hepatic, gastric, renal, etc.—capable of provoking auto-intoxication.

Another phase of this interesting subject was mentioned by Noble[16] of Washington, who refers to the fact that "many striking results follow its administration in failure of metabolism. Small doses of thyroid extract have cleared up, in what appeared to be a marvellous manner, the effect of metabolic poisons. The most striking results were seen in a patient with alcoholic insanity. It was a very pronounced case in which the patient was becoming demented. The patient was put upon 2 grains of thyroid extract, and in four days the symptoms of

dementia entirely disappeared. The drug was stopped, and the dementia reappeared. It was again given, with reappearance of normal intellection."

The Value of Thyroid Extract in Dermatology.—Realizing that many dermatoses are the result of toxæmia, it was not unreasonable to attempt the control of certain skin disorders by associating with the usual local treatment the empirical use of thyroid extract, and a number of very encouraging results have been recorded. Levi and de Rothschild[17] have reported a number of cases of the more intractable forms of skin diseases, including psoriasis, scleroderma, and eczema, that responded to this treatment. Among numerous dermatological indications for thyroid therapy, Morris[18] records a case of keloid, in which thyroid appeared to have been useful. He also states that multiple warts have been found rapidly to disappear under thyroid medication.

The influence of the thyroid upon the nutrition of the skin and its appendages is well known, and disturbances in the nutrition of the scalp, nails, and epidermis have been benefited by the revolution in metabolism brought about by a more or less protracted course of small doses of thyroid extract.

The manner in which the sclerotic conditions of scleroderma and chronic rheumatism have been influenced suggested a possible special action of the thyroid in the control of the conditions of this nature, and as an outgrowth of the application of this idea, Gilbert[19] calls attention to the fact that Leopold Levi has in this manner successfully treated five out of seven cases of Dupuytren's contraction. Following thyroid medication, the indurated tissue became softened, and the function of the hand was regained. It is suggested in an editorial consideration of this subject[20] that "these results point to

a thyroid origin of the contraction of the palmar fascia. This view is borne out by the incidence in these cases of other symptoms of thyroid deficiency—subacute 'rheumatism,' pains, headache, alopecia, œdema, which were also improved by the treatment. . . . M. Gilbert's treatment [really M. Levi's] seems worth a trial."

The Use of Thyroid Extract in Gynæcology.—From an experimental standpoint the influence of the thyroid upon the reproductive organs is decided, but complex. In animals Blair Bell[21] has shown that thyroidectomy produces an intense degree of uterine atrophy, while the ovaries do not retrogress. On the contrary, there appears to be an increase in their activity, especially in the follicles.

The intimate relation of the thyroid and the female reproductive organs has already been referred to, and is one of the endocrinous relations that is most commonly noticed in everyday clinical observation. The menstrual disorders of hyperthyroidism and myxœdema, the influence of certain changes in the reproductive activity, notably pregnancy, upon the thyroid, and other clinical findings, indicate that we may expect a considerable amount of help from the application of thyroid therapy in gynæcology.

The stimulating action of the thyroid on the ovaries has been used to good advantage in the treatment of ovarian insufficiency with its various manifestations—*e.g.*, infantilism, amenorrhœa, scanty menstruation, and even sterility. It is not possible exactly to explain the broad influence of thyroid medication upon this class of diseases: it is far too complex. We can only accept the indubitable clinical results which have frequently been obtained as a stimulus to continue the use of this method of treatment, in the hope that this empirical application

of thyroid therapy may eventually be scientifically explained. Of course, it is no explanation to say that the thyroid, through one of its hormones, stimulates the ovary;* nor can we get much satisfaction out of the statement that thyroid medication seems to re-establish the hormone balance, and thus favourably to influence disorders which really have little or no direct connection with the thyroid itself. The fact remains, however, that in gynæcologic practice thyroid extract has been found to be a most valuable remedy.

A number of writers have recorded good results following the use of thyroid extract in the toxæmias of pregnancy, notably eclampsia and hyperemesis gravidarum; and Thompson,[22] in his consideration of the influence of the thyroid on pregnancy and lactation, shows that lack of thyroid secretion influences sexual activity adversely, and that sexual activity, whether physiological or pathological, causes overactivity of the thyroid. This form of hyperthyroidism is considered by Thompson to constitute an index to the toxæmia of pregnancy, to counteract which the thyroids raise their antitoxic protective power. Abundant clinical evidence supports the theory that the physiological overactivity of the thyroid during pregnancy is a valuable safeguard against the toxæmias incidental to that state.

Thyroid extract is beginning to be used quite often in dysmenorrhœa, for many times the cause of certain disturbances in ovarian action, etc., must be sought in the other endocrinous organs, especially the thyroid. Provided no organic condition, such as stenosis of the cervix, is present, and when the ovaries seem to be sound, Dalché[23] uses small doses of powdered thyroid (0·025 to

* As a matter of fact, evidence has been recorded earlier in this chapter which indicates that under certain circumstances the thyroid exerts an entirely opposite effect.

0·05, or even 0·1 gramme, daily), and continues this treatment for a month or more. This exhibition of thyroid extract frequently seems to restore the normal balance, and a short course of treatment results in the regulation of the incidence and quantity of the flow, as well as in a considerable reduction of the abdominal pain. After the first month he gives the extract during the ten days preceding the date of menstruation. Occasionally ovarian (luteal) extract may be alternated with the thyroid.

Dalché remarks that if by careful treatment and proper hygiene the painful periods are controlled two or three months in succession, the tendency to dysmenorrhœa seems to be broken up, and menstruation proceeds normally thereafter.

The Action upon the Vascular System.—Thyroid extract, like extracts of the adrenal medulla and posterior pituitary body, exerts quite an important influence upon blood-pressure, although it cannot be said to compare with these either in rapidity or extent. Usually it has a slight depressor action, although overdoses of thyroid extract materially increase the pulse-rate, and the pressure may be raised principally by the direct action on the heart, rather than upon the vessels, as with the other preparations mentioned.

In a personal communication the author learned from Beebe that he has recently isolated a substance from the thyroid gland which has a valuable reducing action on blood-pressure. This substance has not yet been named, but has been used clinically by Beebe in a number of cases of hypertension with good results, although nothing definite regarding the characteristics and mode of action of this depressor thyroid hormone have yet been published. He mentioned a case in which the blood-pressure was persistently near 200 millimetres Hg., and by small

daily doses of this " X-substance " it has been reduced to 150 millimetres, and is kept there by occasional injections of this preparation. At present it does not appear that this substance has any of the other characteristics of thyroid extract, but is evidently one of a number of the active principles of the thyroid gland which are known to be present, but extremely difficult to isolate.

The reduction of excessive blood-pressure by means of animal preparations is not at all an easy matter, such as is, for example, the increase of blood-pressure—*e.g.*, with *pituitrin*—and Beebe's discovery bids fair to add another extremely important hormone preparation to the present list.

Nervous Disorders and their Treatment with Thyroid Extract.—The frequent occurrence of disturbances of the nervous equilibrium in patients suffering from thyroid disorders has stimulated much speculation as to the relation of certain nervous and mental disorders to thyroid disease, as well as to the possibilities of thyroid therapy in the treatment of these conditions. We have already seen that thyroid extract has an influence for good upon the mental backwardness of certain individuals, whether suffering from an obvious hypothyroidism or with the minor and usually overlooked deficiency. It seems that considerable benefit may accrue from a course of thyroid therapy in certain forms of insanity in adolescence and the climateric. In some mysterious manner a stimulus is given which often leads to considerable amelioration and even ultimate recovery. In many hospitals for the insane thyroid extract is an important remedy, although in organic diseases it must needs be of very limited value. These facts, however, should lead us the more thoroughly to consider the manifestations of thyroid activity in patients suffering from mental and nervous disorders,

and wherever the least connection can be made between thyroid disorder and the disturbance in question, careful and judicious attempts should be made to influence the conditions by means of thyroid therapy.

Nutrition and Developmental Disorders in Children.—Since many of the disorders of growth are, as we have seen, due to defective thyroid activity, we must expect to find in the literature frequent references to the value of thyroid preparations in developmental disturbances, and this is decidedly the case, for there are a large number of references to numerous phases of its usefulness in this branch of medicine.*

In defective mental and physical development thyroid extract has been used with surprisingly good results both alone and associated with other synergistic drugs or animal extracts. In rickets, and occasionally in osteomalacia, it has been used with varying results, and there are numerous references to its value in the treatment of Mongolism, cryptorchism, infantilism, and other disturbances of growth and development, which may not necessarily be due to an obvious thyroid deficiency or myxœdema.

Another common disorder of children—nocturnal incontinence—in some indefinable way is very often favourably affected by this treatment. Leonard Williams[24] and Hertoghe were the first to make this important application of thyroid therapy, and report some very interesting cases in which the results can only be attributed to this medication since other methods had been tried and proved

* The bibliographic references in this chapter are very superficial and far from complete. So many books and monographs are devoted to this phase of organotherapy, most of which have extensive bibliographies, that it seems unnecessary to take the time or space to do more than connect the essential statements which are the basis of this chapter with the original literature on the various subjects.

futile. The dose suggested is ½ grain (0·03 gramme) twice daily for a child from two to six years, and 1 grain (0·065 gramme) twice daily for a child from ten to thirteen. In younger children ¼ grain is suggested. Ordinarily the condition should be relieved in a week's treatment, but if it proves refractory, it may be alternated with a short course of calomel in $\frac{1}{10}$-grain (0·0065 gramme) doses. This work has been frequently confirmed in the literature of the last two or three years, although as yet there seems to be no definite explanation of the mode of action of the extract in this particular disorder.

The Newer Conceptions of Graves's Disease.—For a number of years exophthalmic goitre has been considered to be a disease of hyperthyroidism, and doubtless in some degree it is; but this conception is changing, and at present it is believed that Graves's disease can no longer be regarded as a simple hyperthyroidism On the contrary, evidence is accumulating to establish the view that the function of the thyroid gland in this disease has been perverted, and hence, instead of classing it as hyperthyroidism, it should rather be called "dysthyroidism," provided this term is used to indicate a change in the proportion of the various constituents of the secretion. Klose[25] has shown that injections of extracts of thyroids taken from cases with Graves's disease cause symptoms very different from those which are produced by the preparations of normal gland.

It is a little beyond the intentions of the present author to attempt to consider a subject of such complexity in other than a very perfunctory manner, and reference is made to it only to call attention to the importance that the hormones play in the causation and control of this disease. It is well to know how to attempt to control conditions of hyperfunction of the endocrinous

organs.* There are certain drugs which are said to have a neutralizing effect upon the thyroid secretion. Principal among these are hydrobromate of quinine, the salicylates, and aspirin. The so-called "neutral hydrobromate of quinine" seems to be best tolerated.

On general principles the X ray has been used, since its influence very materially retards the activity of the ductless glands exposed to it. The thymus gland having been frequently found enlarged or persistent during exophthalmic goitre has been considered to produce a substance which is antagonistic to the thyroid secretion, and is still used in the treatment of Graves's disease (see Chapter XV.).

Extracts of the thyroid gland itself have been used in both stages of this disease: in the condition of hyperthyroidism to diminish the need for the compensatory increase in the size and activity of the gland, and in the stage of hypothyroidism to supplement, in a degree, the diminished secretion. Leonard Williams,[26] referring to this subject, writes: "If I were to be asked if I had any confidence in any drug treatment of Graves's disease, I would reply in the affirmative. I believe in calcium chloride and in thyroid extract; the former in large doses, the latter in small doses. The calcium seems to give the thyroid something to do, and diverts its exuberant activities from undesirable channels into those which are harmless. The thyroid seems to readjust the broken equilibrium, but to do this it must be given in very small doses." He also adds: "If I can assert anything in connection with the thyroid with any degree of dogmatism, it is that Graves's disease is not due to a simple excess of thyroid secretion. That the thyroid is pro-

* A further consideration of the subject of "The Control of Hyperendocrinism" will be found in Chapter XXXI.

foundly disturbed in this condition is obvious enough, but in almost every case there are symptoms of thyroid insufficiency."

Several preparations for the treatment of Graves's disease have been made from thyroidectomized animals. Preparations of the blood of such animals have been used since 1884 with varying results. Principal among the more recent of these preparations are *antithyroidin* (Mœbius), *hémato-éthyroidine*, and *thyroidectin*.

Beebe has evolved a valuable method of treating hyperthyroidism by means of an antiserum produced by inoculating a thyroid preparation into rabbits and sheep. Further information regarding the details of this treatment may be found in his book.* Its value has been demonstrated in more than three thousand cases, and a number of very good results have been obtained.

The administration of all preparations, irrespective of their source and connection with other measures, is rarely followed by uniform results. Sometimes the influence upon the conditions is good; as often it is indifferent. It seems, however, that while surgery has undoubtedly been beneficial in the treatment of Graves's disease, the eventual successful treatment will depend upon hormone influences, and be available through preparations or combinations of animal origin, regarding which we are just beginning to classify our knowledge.

Thyroid Preparations and their Administration.—Naturally there are a large number of preparations of thyroid gland upon the market, and it is quite impossible to refer to all of them. Preparations are now official in the majority of pharmacopœias, and information regarding these may be found in any standard work of pharmacology and therapeutics.[27]

* "The Diseases of the Ductless Glands." (See list of books in Appendix.)

The standardized dried and powdered preparations, preferably in tablet form, are most convenient, and, in spite of numerous excellent proprietary preparations, constitute the major part of the thyroid extract at present used.

Among the proprietary preparations worthy of mention are *iodothyrin*, a preparation brought out by Baumann (who was the first to discover the importance of the iodine content of thyroid extract). It has been spoken of very favourably, but its therapeutic action is hardly that which has been attributed to it, and often, for some unexplained reason, it is less active and not so well tolerated as the ordinary desiccated powder. *Thyroprotein* is one of the best preparations, and is prepared according to the method of Beebe,[28] which is briefly as follows: "The glands are separated from all extraneous tissue, ground up, and extracted with normal saline solution, which has been made slightly alkaline. It is then filtered, heated, and the thyroid nucleoprotein is precipitated with acetic acid. The supernatant liquid is then separated by decanting and half-saturated with ammonium sulphate, to throw down the thyroglobulin, which, according to Beebe, corresponds approximately to the colloid, or fully formed normal thyroid secretion. These two precipitates—the nucleoproteid and the globulin—may be dried and prepared in tablet form, or redissolved and used for hypodermic administration. *Thyroprotein* is a mixture of these two substances standardized to represent 0·33 per cent. of iodine per gramme of fresh gland. The dosage of this preparation differs from that of the usual extract. Tablets of different strengths are prepared. A "1 per cent. tablet" indicates that there is 1 per cent. of the active material in the tablet—*i.e.*, $\frac{1}{50}$ grain in a 2-grain tablet, or $\frac{1}{20}$ grain in a 5-grain tablet. This is a standard dose, and is used

with exactly the same indications and precautions as ordinary thyroid extract; and it has the advantage that it contains the physiologically active portion of the thyroid without the toxic and deleterious substances which are present in the dried extract.

Another preparation of this character is called *thyratoxine*, which is the usual dry thyroid extract deprived of its lipoids, peptones, and bases by extraction and autolysis. It is said to be one of the most active, and at the same time harmless, preparations, and that its administration may be "pushed" without the symptoms of hyperthyroidism which would follow similar doses of the ordinary extract.

Since thyroid therapy has become a comparatively common procedure, there have, unfortunately, crept into the market preparations which are variable and at times inert. It is difficult to detect such preparations by their appearance, and the only way to be sure of getting a good preparation is to see that the name on the bottle is a good one. As we have learned, Osborne hints that a little iodine will render the negative preparations active. It would seem, however, better to secure as perfect a preparation as possible.

Pluriglandular Combinations.—Clinical experience with minute doses of thyroid extract, given in conjunction with extracts from other glands, leads to the supposition that it materially enhances their action. This connection does not necessarily have to be a synergistic one, for Bandler[29] of New York reports that ovarian extract may be advantageously combined with thyroid, especially when used to promote metabolism and encourage oxidation. He incidentally noted that the annoying symptoms occasionally produced by thyroid medication are often greatly diminished by the addition of ovarian extract.

It has been suggested that thyroid extract stimulates the resistance of the system to certain drugs which may be given concomitantly with it. It is at least true that the influence of pluriglandular extracts, of which the small doses of thyroid extract constitute a part (see Chapter XXX.), increases the general reactive powers of the system in a manner which renders them more susceptible and responsive to therapeutic procedures, both medicinally and otherwise. The empirical use of thyroid and other hormone combinations, while essentially "medication in the dark," has undoubtedly justified itself in the hands of many physicians, and further reference to this subject will be found in the chapter devoted to the application of pluriglandular extracts.

Heinrich Stern[30] writes interestingly on the numerous untoward effects that may result from the administration of thyroid, and suggests how to obviate them. He has also suggested a combination of thyroid extract, $\frac{2}{3}$ grain; epinephrine, $\frac{1}{64}$ grain; and sodium cacodylate, $\frac{1}{25}$ grain, as especially suitable for the treatment of alopecia, as he supposes defective growth of the hair to be a symptom of hypothyroidism. Strangely enough this same combination has been also used by him in the treatment of interstitial gingivitis. He believes that the adrenal content of this preparation serves as an antidote against certain of the thyroid toxins.

The Contra-Indications to Thyroid Therapy.—There seems to be a general consensus of opinion that pulmonary tuberculosis is a definite contra-indication to the administration of thyroid extract. All are not agreed on this point, however, and while the use of thyroid extract in tuberculous cretins is manifestly not contra-indicated, it may be used with extreme care in patients known to be suffering from tuberculosis.

Obviously the symptom complex of hyperthyroidism is a partial contra-indication to thyroid therapy, and tachycardia, extreme irritability, and nervousness should be a warning to exercise extreme care if it seems necessary to resort thereto. It has been said, however paradoxical it may seem, that thyroid extract may be used with advantage in some cases of Graves's disease. Naturally the commencement of the treatment is made with extremely small doses.

Glycosuria and diabetes mellitus constitute another indication for special care in the administration of thyroid extract, and in some cases a direct contra-indication against its use. It will be remembered that the thyroid antagonizes the pancreas, and while the influence of thyroid extract upon the sugar elimination in diabetes is not nearly so marked and persistent as that of adrenal preparations, there is no doubt that thyroid extracts may be detrimental in this disease. Garnier and Schulmann[31] have shown that this action may be very marked. An experimental adrenal glycosuria, in which the amount of sugar in the urine amounted to 2·96 grammes, was increased to 5·13 grammes when a double dose of thyroid extract was injected simultaneously with the adrenaline.

The Indiscriminate Use of Thyroid Preparations.—By far the most important contra-indication to thyroid therapy is its indiscriminate administration in numerous serious or insignificant conditions without careful medical supervision. More particularly does this apply to the treatment of obesity, which, while favourably influenced by judicious thyroid therapy, is as often a means of complicating matters because of the much more extended influence of the thyroid extract than upon fat metabolism alone. Thyroid extract is far from being a home remedy, and to gain the best results, its administration requires

even more skill and attention than many physicians at present give to it.

Dosage of Thyroid Preparations.—Thyroid preparations are not harmless, and improper dosage can cause considerable inconvenience, and even organic disease. There has been a tendency to use larger doses than necessary, but in the last five years very frequent references have been made to the necessity of using small doses.

Since practically all thyroid products of reputable manufacturers are standardized to contain a minimum of 0·2 per cent. of iodine, the dosage usually can be easily gauged. Of the standard preparations the maximum initial dosage should be ½ grain (0·03 gramme), and, depending upon the circumstances, this dose may with advantage be reduced to as little as $\frac{1}{20}$ grain (0·003 gramme), or increased to 1 grain (0·065 gramme), or 1½ grains (0·1 gramme) given from two to four times a day.

Apparently insignificant initial doses of thyroid extract are often sufficient to produce the desired favourable effects, and it is much better to give small doses for a longer period than a few large ones.

Leopold Levi[17] has suggested a standard treatment consisting of 10 centigrammes (1½ grains) of desiccated thyroid daily, and advises the administration of this dose for ten days, followed by five days without the drug. Occasionally he gives twice this dose every other day. In cases of decided hypothyroidism or myxœdema the dose must be made to fit the conditions, as with every other organotherapeutic preparation.

Leonard Williams,[26] in this connection, emphasizes the need for small doses. He says: "Doses of 15 grains a day or even 5 grains a day, apart from any mischief that they may work, will defeat their own purpose, for this peculiar principle is quite established in my mind

that you can produce the symptoms of thyroid insufficiency by overdoses of thyroid extract."

Overdosage of thyroid extract is shown by a slight rise in the temperature, and an increase in the pulse-rate, and later by dizziness, headache, nausea, occasional tremors in the fingers, and a general feeling of restlessness. Such signs indicate a complete stoppage of the treatment for some days. It has been suggested that the coincident administration of arsenic reduces the possibilities of inconvenience from thyroidism.

In myxœdema and cretinism the dosage necessarily varies. Enough of the substance must be given to control the cretin manifestations and to replace the missing secretion. In some cases 5 grains of the extract daily suffices, in others as much as 15 or 20 grains needs to be given. The original case first treated in England by Murray is still alive and continuing her thyroid medication. Recently he referred to this case, and writes[32]: "The condition of health is being maintained by a dose of 10 minims of liquid thyroid extract each weekday, or 6½ ounces in the course of a year. Less than a gallon of thyroid extract in all has therefore maintained her in health for twenty-two years. No variation of the dose has been found necessary. In some cases the best results can only be obtained by adjusting the dose from time to time according to physiological requirements, in a manner which some patients learn to do accurately for themselves."

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CHAPTER XIV

THE CURATIVE PROPERTIES OF PARATHYROID EXTRACTS

The Parathyroid Hormone—The Detoxicating Powers of the Parathyroids—The Relation between the Thyroid and the Parathyroids—The Influence of the Parathyroids on Calcium Metabolism—Calcium in Cellular Hyperexcitability—Parathyroid Therapeutics—The Treatment of Paralysis Agitans—Puerperal Eclampsia—A Parathyroid Element in Epilepsy—Tetany—Other Uses of Parathyroidine—Combining Parathyroid with Other Glandular Extracts—Dosage and Administration.

From the standpoint of anatomy, the parathyroid glands are, perhaps, the most insignificant of all the organs of internal secretion, yet it is no exaggeration to say that their hormone influence is comparatively greater than that of any other of the endocrinous organs. Their influence in physiology and the possibilities of their therapeutic value have only recently been considered; and this is not to be wondered at when we recall the ignorance of the whole subject of glandular therapeutics, say, twenty years ago. As a matter of fact, this set of organs was entirely overlooked until Sandström[1] of Upsala discovered them in 1880. Even this important discovery was incomplete, for he had only found the pair now termed the "external parathyroids," and it remained for Kohn[2] to locate and describe the so-called "internal parathyroids" fifteen years later. These glandules are occasionally called the "epithelial bodies," the name

being a translation of the German term used to designate the parathyroids.

Of the numerous experiments in which two, three, or the whole of these glands were removed, and the resulting disturbances, of the physiologic relation between the parathyroids and other glands, and whether their removal is followed by a compensatory hypertrophy elsewhere, we can only briefly write. It forms the basis of a most extensive literature, and since it does not strictly concern therapeutics, it must be passed over, although, of course, all the facts thus established are concerned in the groundwork of our present knowledge of the therapeutic value of parathyroid extracts. We are still in the early stages of this special knowledge, and there is doubtless much more to be learned which will prove of eminently practical usefulness. It seems quite clear that, in spite of their apparent insignificance, the parathyroids must be considered absolutely essential to life, and that their principal service to the organism lies in their power to destroy certain toxic wastes which seem to have a special predilection for the nervous tissue. It has been experimentally shown that these substances produce, by their action as well as by the removal of their benign influence, a series of nervous manifestations, the principal of which is the symptom complex termed "tetany."

The Parathyroid Hormone.—It is generally agreed that the principal source of the activities of the parathyroids is a hormone which is distributed by the blood to the appropriate tissues, although it is not impossible that these glandules may produce antitoxic substances which neutralize, attenuate, or destroy products which, if allowed to remain, would be harmful.

In discussing the chemical activators in his presidential address before the British Association in 1912, Sir E. A.

Schäfer[3] said: "The case of the parathyroid glandules is still more remarkable. They are four minute bodies, each no larger than a pin's head, embedded in the thyroid. Small as they are, their internal secretion possesses hormones which exert a powerful influence upon the nervous system. If they are completely removed, a complex of symptoms, technically known as 'tetany,' is liable to occur, which is always serious, and may be fatal. Like the hormones of the thyroid itself, therefore, those of the parathyroids produce effects on the nervous system, to which they are carried by the blood, although the effects are of a different kind."

Not only is the parathyroid hormone essential to normal metabolism, but it is available as a therapeutic agent, and, as will shortly be shown, its detoxicative powers make it indeed a most valuable weapon.

The Detoxicating Powers of the Parathyroids.—It may be that the parathyroid hormone activates certain tissues —as, for instance, the thyroids—to produce antitoxic bodies; or, on the other hand, it may have a direct destructive action upon these poisonous substances. However this detoxicating action may be accomplished, it is of considerable interest, for upon it is based practically every phase of parathyroid therapy.

The importance of this factor is emphasized by the recent work of Koch[4] in the laboratories of the University of Michigan. He discovered certain toxic bases in the urine of parathyroidectomized dogs. In every case methylguanidin was found, and, where the amount was smaller than usual, other bases, such as cholin, neurin, etc., were present.

As a result of his findings, Koch suggests that "the parathyroid internal secretion appears to be concerned also with anabolic processes related to the synthesis of

nuclear contents." Whether or not such a hypothesis can be further substantiated remains to be seen. In any event, the final isolation of recognized toxic chemical products of traceable origin has paved the way to definite conceptions and specific lines of inquiry, where hitherto the explanations have been vague and the outlook unpromising.[5]

The Relation between the Thyroid and the Parathyroids.—It must be borne in mind that the parathyroids are not connected with the thyroid, certain statements to the contrary notwithstanding. Their similarity in name and their anatomic proximity are liable to be misleading. The parathyroids are quite distinct bodies, differing from their neighbour in origin, structure, and action. It has also been shown that there is a difference in their chemical composition, as, unlike the thyroid and the thymus, they contain no iodine.

However, there certainly is some connection, just as the other endocrinous organs are related, although there are diffences of opinion on this subject. Gley[6] has made some very decided statements to the effect that these organs are physiologically intimate, and states that total thyroidectomy is followed by a compensatory hypertrophy of the external parathyroids. This position is supported by numerous writers, while Walbaum[7] believes that these glands are antagonists; but Gley has since shown that tetany can be made to disappear by injecting thyroid extract. This position is rendered rather complicated, since Gley's deductions are contradicted by Blum, Pfeiffer, and others.

Jeandelize suggests that, while the thyroid promotes metabolism, the parathyroids co-operate with it only in that they render innocuous the toxic by-products of metabolic activity.

Moussu[8] has consistently declared that the parathyroid function is distinct and different from that of the thyroid, the chief effects of the latter being of a trophic character, while the former are of an antitoxic nature. There is a considerable difference between the cachexia strumipriva which follows thyroidectomy and the condition following parathyroidectomy. This difference extends to the reaction of the body to parathyroid extracts. Moussu found that the symptoms of thyroidectomy are not controlled with parathyroid extract, but that sufficiently large doses of this extract cause the tetany which follows parathyroidectomy completely to disappear. This he considers to be further evidence of the independence of these two organs.

Rudinger[9] seems to have given the most reasonable explanation of the interrelation of the thyroid and parathyroids. He concludes that — (1) Thyroidectomy is followed by parathyroid hypertrophy; but (2) the manifestations of hyperthyroidism (exophthalmic goitre) are diminished by parathyroid treatment, while hypothyroidism (myxœdema) is made worse; (3) tetany follows thyroidectomy, but the effects are less marked than those following parathyroidectomy later; and, finally, (4) parathyroidectomy is followed by a degree of thyroid hypertrophy. The difference of opinion between experimenters is seemingly due to the fact that there may be accessory parathyroids in the thymus and elsewhere, and the operations have not always accomplished just what was intended. Biedl[10] writes: "I have found in numerous cases that the removal of the thyroid, together with the internal parathyroids, is nearly always followed by hypertrophy of the external parathyroids. The hypertrophy is more or less clearly marked according to the length of time after operation. The reason for this seems obvious, and may

be an explanation of the statements preceding. With thyroidectomy, the hypertrophy of the external pair of glands is Nature's effort to replace the removed internal pair."

Evidently, then, the intimacy of these glands is established, although it is equally clear that they are only associated and not actually connected in any way.

The Influence of the Parathyroids on Calcium Metabolism.—There seems to be an intimate connection between the whole of the endocrinous system and the metabolism of calcium salts. Elsewhere several facts have been recorded to substantiate this, and here a few words must be said as to the influence of the parathyroids upon this special phase of metabolism.

MacCallum[11] and his associates have made a special study of this subject, and conclude that the hyperexcitability which is the principal symptom of parathyroid tetany is produced by the withdrawal of calcium from the cells.*

This is a partial explanation of the frequency of acidosis in parathyroidectomized animals. Since there is not enough calcium to neutralize the carbamic and other acids, the accumulation results in uræmia, convulsions, etc.

Calcium in Cellular Hyperexcitability.—Convincing evidence of the value of calcium medication is furnished by

* Ringer and Loeb have shown the importance of certain of the metallic ions in the maintenance of cellular activity. These elemental substances are an essential and integral part of the cell protoplasm, and a predominance of one or another of these electrolytes materially influences the activity and reactivity of the cells. For example, nerve and muscle cells are stimulated in direct ratio to their sodium content, while calcium exerts a diametrically opposite effect. In other words, the increase of the calcium content of the cell is accompanied by depression, while the diminution of calcium causes an excitability which may reach serious and pathological proportions if the amount of calcium electrolytes is reduced below a certain minimum.

Williams[12] considers the relation of the ductless glands to calcium metabolism in a very lucid address on arterio-sclerosis which is well worth reading in full.

MacCallum and Voegtlin[13], Frouin, and others, who show that injections of solutions of calcium salts into parathyroidectomized animals very promptly control the manifestations of tetany. Edmunds[14] and others have found that the administration of large doses of calcium prevents the tetanic results of thyro-parathyroidectomy. From this a valuable suggestion may be drawn as to the importance of studying the urinary acidity, the other evidences of acidosis (acetone, etc.), and the calcium content of the blood, in all cases where there is a cellular hyperexcitability, whether supposedly parathyroid in origin or not. The present author's research work with the urinary acid index[15] has convinced him of the extreme importance of acidæmia in everyday practice, and in the clinical investigation of those suffering from Parkinson's disease, chorea, epilepsy, or other allied diseases, it will be surprising how often the urinary acidity is from 200 to 500 per cent. above the normal.

Another point is deserving of mention here. Calcium therapy can often be coupled with the use of animal extracts, and particularly parathyroid extract. This combination is not empirical, and each element is complementary to the other. The calcium helps to replace that which has been lost by the cells, which loss, we have seen, is often accompanied by cellular hyperexcitability; while the parathyroid extract, in addition to any direct influence that it may have, favours the re-establishment of the lost calcium balance by the regeneration of the normal parathyroid activity where this is possible.

Parathyroid Therapeutics.—All the available literature dealing with the use of parathyroid extract indicates that its value is dependent upon a marked antagonistic action which it seems to exert on certain metabolic toxins. The action of these extracts coincides with the physiologic

activities of the glands, and has been successfully applied in the treatment of such diseases as tetany, paralysis agitans, hyperthyroidism, eclampsia, epilepsy, chorea, etc.

The Treatment of Paralysis Agitans.—Berkeley[16] of New York has worked with those extracts for eight or nine years, and his principal study has been their application in the treatment of Parkinson's disease. In his latest paper[17] he states that this form of medication "has wrought a revolution." This writer has brought forward several plausible considerations which indicate that there is a relation between paralysis agitans and parathyroid pathology, and, best of all, he backs them up with numerous reports of evidently successful results.

In as progressive disease as this, it is clear that treatment must be persistent in order to be successful. If benefit is found, it manifests itself just as does the disease itself—slowly and gradually. If small doses—$\frac{1}{60}$ grain of purified parathyroid extract once or twice a day—are given over a period of months, there are good chances of success. The cases reported by Berkeley are convincing, and his experience with a large number of patients, "now well up in the hundreds," shows that benefit has accrued in over 80 per cent. After some weeks, sometimes months, one notices a gradually lessened muscular rigidity and bettered muscular control, diminished pain and tremor, and the abolition of drooling. Often the distressing insomnia is controlled. This writer is most insistent that *real* parathyroid extracts must be used, and states that "apparently bits of lymph nodes, thymus, accessory, thyroid, and even fat have done duty in many laborious experiments." It seems quite possible that the failures —for, of course, the inevitable failures and depreciations of this method have appeared in the literature—are due

to carelessly prepared and consequently inactive extracts. Berkeley explains his methods of locating the glands, and states his preference for those taken from the ox.

These interesting statements do not all come from a single source, and Berkeley's treatment is becoming more generally used. Alquier[18] has made several communications in which he tells of the good effects of this method of treatment. It seems that, contemporaneously with Berkeley, Lundborg[19] was studying this subject in Sweden. He came to the conclusion that paralysis agitans and the other motor neuroses—Thomsen's disease and myoclonia —are due to hypoparathyroidism.

It seems as though the parathyroid treatment of Parkinson's disease has a sound physiologic basis, and is rational and deserving of the study of and clinical application by the profession generally.

Puerperal Eclampsia.—Several investigators have applied the fundamentals of parathyroid therapy in the treatment of other severe toxic states. Vassale[20] of Turin lays stress upon the value of this medication in puerperal eclampsia. In certain cases this treatment has controlled the convulsions, and Vassale inclines to the idea that there may be a parathyroid origin of eclampsia. His results have warranted a belief that large doses of parathyroid extract are useful in eclampsia in the same ratio as thyroid extract is useful in myxœdema. This is a sanguine view, but not to be dismissed on that account. In his researches Vassale makes formal distinctions between the antitoxic functions of the parathyroids and those of the thyroid. He calls attention to the fact that parathyroid insufficiency may be congenital, and may also follow pathologic processes in these glandules. It seems that this insufficiency is quite compatible with ordinary existence, but, should there come an incident—

as, for example, obesity, accouchement, chronic eczema, etc.—the convulsive phenomena somewhat similar to tetany promptly appear. There is no doubt that very slight straws are sufficient "to break the camel's back," and others have shown that seemingly slight pathologic changes in the parathyroids are not infrequently found in patients dying with tetany, paralysis agitans, eclampsia, etc.

A Possible Parathyroid Element in Epilepsy.—Vassale suggests that the other convulsive conditions not infrequently met with in general practice may all be associated with parathyroid insufficiency, and gives weight to his contention by reporting two cases of epilepsy which were controlled by this form of medication. This was apparently first suggested by MacCallum[21] of New York, who in 1903 intimated that there might be a connection between parathyroid disorder and epilepsy. Naamé gives his conception of epilepsy as a disorder due to organic hypoparathyroidism. Perhaps this might be better termed a "parathyroid dystrophy," since this writer's idea is that in epilepsy the parathyroids do not accomplish their antitoxic function, and that certain metabolic poisons, which electively influence the nervous system, are allowed to accumulate until a violent reaction to their presence is brought about—the seizure which is pathognomonic of epilepsy. His theory is very interesting, and he reports having put it into practice in numerous cases over a period of some years with most encouraging results. A résumé of his paper[22] is worthy of a place here:

There can be no doubt that the manifestations of epilepsy are of a toxic nature. The atonic and tonic convulsions of the crises, the rise in temperature often noted at these times, the frequent and severe headaches, and the profound prostration, all point to this. Naamé

suggests that the parathyroids, because of an intermittent disability ("*claudication intermittent*"), are unable to detoxicate the system. Bearing in mind the secretory antagonisms of the gonads and parathyroids, we see a possible reason for the frequency of epilepsy at puberty. There is indubitable evidence that there is a relation between epileptic crises and the genital functions. Fits are intensified at the menstrual periods, and, on the other hand, are considerably diminished during pregnancy. The prescription that Naamé suggests is as follows:

Parathyroid extract	0·03	gramme
Thyroidine	0·003	,,
Sacch.-lact. ad.	0·10	,,

M. ft. One cachet. Administer during the seizure, or, preferably, the premonitory symptoms, two or four daily.

"Under the influence of this treatment," continues this writer, "I state it definitely, in the cases which I have watched in patients whose age is over twenty, the crises are rapidly suppressed and reduced to a simple vertigo. They become rare and benign, without incontinence of urine or tongue-biting, and neither headache nor prostration follows. Further, the humour of the epileptic changes. He enjoys life, his memory is better, and his intelligence clearer."

Does this apply to all forms of epilepsy? It is not likely. Naamé proceeds: "After having eliminated traumatic epilepsy and that which is a sequel of meningitis, I will say that the epileptic who observes the rules of hygiene and submits himself methodically to the treatment given above, should not have fits—that is to say, he can be functionally cured. As far as an anatomical cure is concerned, it is conditional. If the parathyroid lesions are definite and of long standing, the reparative process may not be fully accomplished, and a degree of

parathyroid insufficiency will remain. But if the epilepsy is recent, and not severe, the glands may respond to the treatment, and perhaps return to a quasi-normal anatomic condition, especially if the treatment is patiently continued."

Tetany, whether post-operative or epidemic, is now considered to be the result of parathyroid insufficiency, and the results of the parathyroid treatment of the tetany of parathyroidectomized animals have been usually decisive. Several reports laud this method, but, fortunately, the disease is so rare that opportunity to test the treatment is not often obtained. It seems that parathyroid extract should always be added to the sedation, hydrotherapy, and rest, which constitute the usual treatment recommended for this disorder.

Other Uses of Parathyroidine.—A number of other reports of the efficiency of the parathyroid treatment are to be found. The majority of these are of Italian origin, doubtless due to the fact that practically the only European preparation is the *paratiroidina* of Vassale. Chidichimo[23] records his experiences with this preparation. Simonini reports having secured favourable results in the treatment of five cases of chorea, and praises this method. More recently Meriggio[24] has contributed a lengthy outline of his experiences with parathyroidine (Vassale). He used it in eclampsia, chorea, uræmia, and toxic states which were accompanied by convulsive seizures. Many of his experiences with it were encouraging. Salvioli and Carraro[25] also discuss the action and clinical possibilities of this treatment.

Combining Parathyroid with other Glandular Extracts.—Attempts have been made to reinforce parathyroid extract with other endocrinous substances, on the admittedly sound theory that there are distinct synergisms and

antagonisms among the hormones. Naamé has recommended the addition of small doses of thyroidine in epilepsy (*q.v.*), while Berkeley impresses the fact that thyroid extracts are distinctly contra-indicated in Parkinson's disease, and hints that failures in the application of his parathyroid treatment may not only be due to inactive preparations, but that thyroid extract may aggravate the conditions. This same author found that the pancreatic, duodenal, and adrenal hormones do not synergize with the parathyroid—at least, in the treatment of paralysis agitans—but that pineal extract, so far, seems to have produced "relatively happy results."

Bearing in mind the presumed physiologic action of the parathyroid hormone—that of *detoxication*—it would seem that extracts of the liver might be usefully combined. Morel,[26] whose work on the physiology of the parathyroids is of a very high character, and whose book[27] is a most interesting résumé of the knowledge on this subject, recently outlined certain functional relations between the liver and parathyroids, and in this paper[28] summarizes these points as follows: As a result of experiment, a close relationship between the parathyroids and the liver is manifested: (1) Anatomically: After the parathyroidectomy the most constant and precocious manifestations are localized in the liver. (2) Clinically: The incidents following parathyroidectomy recall those following physiologic exclusion of the liver. (3) From the biochemical viewpoint parathyroidectomy in the dog causes acidosis, excessive elimination of urinary nitrogen, and diacetic acid, as well as diminished power to utilize dextrose, and carbamic intoxication. (4) From the therapeutic viewpoint it is shown that hepatic opotherapy—(*a*) increases (almost doubles) the life of the animal deprived of the parathyroids; (*b*) diminishes convulsions, anorexia, vomit-

ing, and asthenia, and benefits the general condition; and (*c*) brings about an abundant diuresis.

Schiötz,[29] in a study of the relation of the internal secretions to cataract, seems convinced that the parathyroids may be connected with this disorder. He says: "It has already been established beyond question that parathyroid insufficiency may lead to cataract." This may or may not be the case. At least, it does not seem to be a settled fact so far as the literature is concerned, but it shows possibilities which have not by any means become generally appreciated. And if parathyroid insufficiency is a factor in the causation of cataract, may not the use of parathyroid extracts be of possible service in its treatment? There is yet much to be done in this special field of research.

Dosage and Administration.—The dosage of parathyroid extract varies very considerably, for, unfortunately, preparations are very often inactive. Berkeley's experiences, already referred to, indicate the difficulty of securing an effective preparation. Undoubtedly a share of the indifferent results reported must be laid to indifferent preparations, but this should not deter the prospective user, for the method is undoubtedly good. Carnot[30] has evidently found that the collection of parathyroids from the abattoirs is no sinecure, and adds: "Il est inévitable qu'il y ait erreur ou fraude dans leur récolte."

The dried extract represents approximately one-sixth by weight of the fresh gland. The glands are best secured from the ox, although Hallion[31] believes the external parathyroids of the horse to be most suitable. In England or America this is not convenient, but, of course, in France and Belgium circumstances are different, since horse-meat is an "article de dégustation de tous les jours."

The average dose of an active preparation, such as that recommended by Berkeley (made by Perry of New York) is $\frac{1}{120}$ to $\frac{1}{60}$ grain (0·003 to 0·001 gramme) once or twice daily over a long period. In acute cases (eclampsia), $\frac{1}{120}$ grain may be given every four hours for four or five doses. Hypodermic preparations are occasionally used, the usual dose being $\frac{1}{60}$ grain.

Vassale's preparation is in liquid form, each c.c. of which corresponds to 0·01 gramme of fresh substance. The usual dose is 1 to 2 teaspoonfuls (4 to 8 c.c.), or a little less than 1 grain of the fresh gland.

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CHAPTER XV

THE THYMUS

The Function of the Thymus—Is there a Thymus Hormone?—The Relation of the Thymus to other Endosecretory Glands—The Thymus, Calcium Metabolism and Growth—Thymus Extract in Malnutrition and Delayed Development—The Thymus Treatment of Simple Goitre—The Influence upon Exophthalmic Goitre—The Possibilities of Thymus in Chlorosis—A New Method of Treating Rheumatoid Arthritis—Contra-Indications.

THE development of the thymus gland in the fœtus and early childhood, and its subsequent retrogression and eventual disappearance* in adult life, indicate that the part played by this organ is concerned in the formation of the body. Occasionally the thymus may be divided, and small areas of thymus tissue may be found separated from the principal gland. These "aberrant" glands, however, are not common.

Pende[1] of Palermo believes that he has discovered a hitherto unknown internal secretory gland which he is able to find with ease in new-born puppies. This gland is, of course, small, and lies above the thymus close to

* The majority of physiologists assert that the thymus normally disappears at or soon after puberty. Not all, however, agree with this. Morel[2] states that in man the thymus is a constant and permanent organ, but that it has a rapid evolution. It weighs about 5 grammes at birth, 2 grammes at about three years, and at about the fourth year commences its normal involution, which is not completed until the twentieth or twenty-fifth year. The thymus does not disappear; there remains, at least, a fatty vestige (the retrosternal body of Waldeyer). More often there is persistence of glandular elements, which in certain pathological circumstances are the seat of a remarkable degree of regeneration.

the thyroparathyroid combination, but is easily differentiated from these organs, the thymus, and from chromaffin tissue. He supposes this gland to have some endocrinous function, and it may be that future research may develop its importance in physiology, pathology, and therapeutics.

The Functions of the Thymus.—Experimental proof of convincing accuracy shows that the thymus is, in its period of activity at least, an essential organ, and while not all cases of thymectomy are fatal, every case thus operated on manifests well-defined symptoms, some of which can be modified by thymus organotherapy. Lampé[3] of Halle gives a very interesting representation of this subject, from both the anatomical and the physiological viewpoints. The experiments of various investigators are reported, and the results are summarized as follows: The thymus gland is an organ of vital importance, as extirpation at the height of its development results finally in death. Probably its most important function consists in the inhibition of acids, and the consequent removal of injurious substances from the blood. This supposed function gives an explanation of the disturbances occurring in the calcium metabolism after extirpation of the organ, as well as for the changes in bone and in the central nervous system. The thymus gland, during its stages of importance, occupies a dominating position over the lymphatic apparatus. Between the thymus on the one hand, and the various organs of internal secretion on the other, complex relations exist. This is especially true of the spleen, for this organ is, so to speak, " prepared " by the thymus to take up some of the latter organ's still unexplained functions after its involution.

Is there a Thymus Hormone ?—It seems quite reasonable to suppose that the influence of the thymus is due to

a hormone, for it is undoubtedly brought about through the blood. Thymus grafts will take the place of the ablated organ, and dried extracts of the gland exert an undeniable therapeutic effect in spite of Starling's[4] statement that "the effect of extracts made from the thymus do not differ from those of extracts made from any other cellular organ."

Biedl,[5] in referring to the blood coagulating powers of thymus extracts, calls attention to the fact that thymus extract remains active after boiling, and this shows that its active principle is not in itself a ferment, but that it is a substance which causes the formation of a ferment having the property of coagulating blood. It will be remembered that the majority of the hormones are also heat-stable bodies.

The Relation of the Thymus to other Endosecretory Glands.—During the period of activity, the thymus is an integral part of the endocrinous system, and has been shown to be an important factor in the maintenance of the hormone balance. Its relation to the other ductless glands is beginning to be better understood,[6, 7] although for a long time it was considered to be a part of the system of lymphatic glands which are scattered throughout the body. That it is connected with the lymphatic system is undoubted, and numerous facts have been brought forward to show this. Poensgen[8] has recently outlined the evidence of reciprocal relations between the thymus, the thyroid, and the lymph glands, and Magnani[9] has shown that the work of the thymus is related to that of the spleen.

The connection between the thymus and the gonads is, perhaps, the best understood at present. It has been noticed with comparative frequency that the reproductive glands do not develop properly until the thymus has

atrophied, and there is a relation between these organs in normal growth as well as in pathologic physiology. Whether the gradual reduction and final absence of the thymus internal secretion permits the development of the gonads, or whether sexual growth with the introduction of the hormones of the generative glands causes the thymus retrogression, is a mooted point. Noël Paton[10] intimates that both factors are concerned, for ovariotomy causes thymus hypertrophy, even after the normal atrophy has occurred; and thymectomy in male guinea pigs is followed by rapid development of the gonads.

There may be still other interrelations between the thymus and other members of the endocrinous system, although the proof is not yet very clear. Adler[11] has intimated that there must be a relation between the thymus and the chromaffin system.

The Thymus, Calcium Metabolism, and Growth.—The belief is becoming quite general that the thymus is concerned in the retention of calcium salts by the body, and, particularly, that it has an influence upon the ossification of bones. In proof of this is offered the experiments of Basch[12] and others, who found that thymectomized animals suffer from marked softening of the bones.

Klose and Vogt[13] report the results of removing the thymus from fifty-four dogs. In the first two or three months there was an increase in weight as compared with the control animals. The psychic condition was modified, and they grew very fat; but soon the weight began to fall, and the so-called "cachexia thymipriva" gradually supervened, and with it a form of idiocy known as "idiotia thymica." Spontaneous fractures, osteomalacia, and rachitis were frequently seen, and the evident common cause was a great want of calcium in the thymec-

tomized organism. The cause of the deficiency of calcium and the idiocy is presumed to be an acidosis.* Klose holds the view that the thymus also is the chief organ for the synthesis of nuclein.

Sommer and Florcken[14] showed that thymectomy in dogs caused the body to become unwieldy and improperly developed. They also found that a thymus graft obviated the developmental changes in such animals.

According to Ott,[15] "the removal of the thymus permits the lower building stones of the organism—perhaps a great excess of the incombustible phosphoric acid—to circulate in the blood. The acid dissolves the calcium salts, or holds them in solution. Artificially produced fractures do not unite with callus, but only with connective tissue."

Sajous[16] states that the function of the thymus is to supply the excess of phosphorus in organic combination required during the growth of the body, particularly while the development of the osseous and nervous systems demands such reserve. This has been sustained by the recognized facts that certain diseases of childhood and adolescence, especially marasmus, rachitis, and trophic disorders of the brain and nervous system are due in part to derangement of the thymus.

Thymus Extract in Malnutrition and Delayed Development.—With such important nutritional factors under its control, the thymus would naturally be expected to be disturbed in pathological states of nutrition and develop-

* From the literature which has been collated in this book, it will appear that calcium metabolism is intimately related to the work of the internal secretory organs. The evidence is somewhat confusing, since so many of the individual endocrinous glands are concerned in this particular phase of metabolism; for, in addition to the thymus, the adrenals, parathyroids, spleen, and ovaries have been definitely connected with this. In Chapter XIV. will be found further information regarding the importance of calcium metabolism, as well as certain therapeutic deductions that can be made from these rather complicated facts. (See especially p. 220.)

ment, and such is unquestionably the case. The importance of the thymus hormone upon metabolism is the basis of its administration in several nutritional disorders of children. It may also exert a beneficial effect in delayed development. Kerley and Beebe[17] report a remarkably interesting case which is an illustration of the action of thymus medication in developmental disorders. A boy of sixteen had the apparent development of a ten or eleven year-old child, but was mentally bright. Nine months' treatment with rest, diet, arsenic, etc., made no material difference; but 15 grains (1 gramme) of thymus extract each day soon caused an increasing height and evidences of sexual development, and within one year this was normal; and the increase in height in eighteen months amounted to 4 inches.

Stoppato[18] secured good results from this treatment in children suffering from rickets; and Mendel[19] insists that the persistent thymus treatment of rickets is encouraging. He even secured good results in cases where the improvement so necessary in general hygiene could not be properly maintained.

Castaigne, Gouraud, and Parisot[20] bring evidence to support the belief in the value of the thymus treatment of the dystrophies of children. They state that it raises the strength and resistance, and stimulates, in a considerable degree, the physical development in rickets, athrepsia, marasmus, malnutrition, etc. This influence is said to be due to important modifications which are brought about in the metabolism, especially of calcium and phosphorus.

The Thymus Treatment of Simple Goitre.—It was in 1895 that thymus was first used by Owen in the treatment of exophthalmic goitre (*q.v.*). It is reported to be of considerable service in the treatment of simple goitre.

An advantage which this form of medication has over the usual thyroid treatment is that improvement can be secured without running the risk of thyroidism, palpitation, loss of weight, etc. It is by no means in general use, although many cases are on record in which the administration of thymus has produced improvement when the previous thyroid treatment had failed or produced unfavourable results.

Shortly after Owen's original communication, Mikulicz[21] reported the results of treating eleven cases of simple goitre by means of thymus extract. At the 1895 Congress of German Surgeons he gave statistics of his work, and the records showed that 30 to 75 grammes of calf's thymus were used daily, and of the eleven cases thus treated, ten were successful. Since then, in Germany, the thymus treatment of goitre has been called "Mikulicz's method." From that time many have tried thymus therapy, and numerous successes and failures have been reported.

The Influence upon Exophthalmic Goitre.—In exophthalmic goitre, thymus therapy has proved very efficient in the hands of Owen[22] and others. It was by accident that Owen first used thymus extract.* He ordered a preparation of thyroid for a case of exophthalmic goitre, and the butcher in error sent up thymus. The effects were remarkably good, and as a result of this fortunate mistake, Owen was stimulated to make a further investigation, and later was able to report four more cases which were considerably benefited by thymus treatment.

A few years later Kinnicutt[23] collected sixty-two cases of exophthalmic goitre treated by this method. In

* It appears that this was the first recorded clinical application of thymus therapy.

thirty-six cases improvement of varying degree occurred, in twenty-five there was no improvement, and in one there was an aggravation of the symptoms. After nearly twenty years S. Solis-Cohen[24] states that he prefers thymus extract to all other organotherapeutic preparations in the treatment of exophthalmic goitre. Of course, he does not confine the treatment to this medication alone, although, save for a local iodine ointment, his recommendations are confined to diet, hygiene, and hydrotherapy. Solis-Cohen uses 7½ to 45 grains (0·5 to 3 grammes) per day in divided doses, and continues this for months. It is especially useful in advanced cases, when all other remedies have failed to bring about improvement, and its beneficial influence seems to act more particularly upon the nervous system of the disease without affecting the exophthalmos.

MM. Dor of Lyons[25] are enthusiastic about the value of thymus extracts. One of them writes that "nothing ameliorates exophthalmic goitre like thymus"; while numerous other authors might be cited to give emphasis to the reputed value of persistent thymus medication in diseases of the thyroid gland.

Hirsch[26] advocates this method of treatment, and reports that *thymin* (tablets made from the thymus of the calf) causes an improvement in the restlessness and sleeplessness, a regression of the struma, reduction of the exophthalmos, as well as a lessening of the cardiac disturbances. She states that improvement was noticed in two cases in which operation had been without effect. Hirsch recommends *thymin* as a soporific, and gives it in doses of one or two ½-gramme (7½ grains) tablets in certain cases of diabetes insipidus, neurasthenia, arterio-sclerosis, and dyspepsia. No untoward action has been noticed, and in animal experimentation, two daily doses of *thymin*

of 0·5 gramme each, produced an increase of nitrogen metabolism.

The Possibilities of Thymus in Chlorosis.—A record of the work of Blondel, who pointed to good results with thymus treatment in the chlorosis which occurs during the period of puberty, deserves to be mentioned. He regards chlorosis as an intoxication by certain products of metabolism which normally should be neutralized by the ovarian secretion. During the earlier stages of development, before the ovaries are functional, or when their function is still slight, these products may give rise to chlorosis unless prevented by the activity of the thymus gland. Starting on this hypothesis, Blondel[27] gave chlorotic girls, for months at a time, 10 grammes (150 grains) of the fresh gland daily, and records that improvement followed. Since then the dried substance has been used with moderately good results.

A New Method of treating Rheumatoid Arthritis.—As a result of the clinical and laboratory work of Nathan of New York,[28] it seems clear that thymus extract may be useful in certain cases of chronic rheumatic arthritis. He advises that all previous measures should be discarded before beginning this treatment; and suggests that there is absolutely no necessity for restricting the diet. Rest, a nutritive diet, and thymus medication will nearly always relieve the more active symptoms in the milder cases; but in severe and intractable cases treatment should be continued for months. The cases reported seem most encouraging, many hopeless bedridden patients being markedly benefited. Nathan thinks that "it is certain that when the thymus is taken conscientiously for a long time, and the patient otherwise judiciously handled, marked improvement, if not perfect cure, can always be expected."

Delany[29] has had equally good results. He admits that this is empirical medication, and says that "desiccated thymus gland . . . has proved a great boon, at least in relieving pain and in checking the progress of the disease." He continues: "The medical profession is not quick to accept such innovations, yet when we feel that relief is obtained, we prefer to have it, even though it is not directly in line with our usual trend of thought. We begin with one 5-grain tablet four times daily, and give an additional tablet every sixth day, until the general symptoms are relieved; then the drug is continued at that dosage, which is usually about 35 grains per day. There is no appreciable systemic reaction to the drug, and it seems to be tolerated alike by young and old."

Nathan states that the attainment of success with the thymus treatment takes considerable time, and requires both persistence and good judgment, as well as careful attention to detail.

Contra-Indications.—Thymus extract is not especially toxic. In some cases as much as 3 or 4 grammes (45 to 60 grains) may be taken daily without inconvenience. It is, however, rich in nucleins, and some have stated that it is not advisable to give it to patients with the uric-acid diathesis, as it is likely to aggravate the gouty symptoms.

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CHAPTER XVI

RENAL OPOTHERAPY

The Basis of Renal Medication—The Evidence against an Internal Secretory Function—The Therapeutic Value of Kidney Extracts—Disadvantages of Fresh Preparations—The Reduction of Albuminuria—Renal Insufficiency and Uræmia—Treatment with Serum from the Renal Vein—Kidney Substance an Adjunct Remedy.

The evidence concerning the supposed internal secretory capacity of the kidneys is most conflicting. Many authorities insist that the kidneys, like numerous other secretory organs, evidently have a supplementary function in addition to their powers of excreting the various effete materials which they are known to pass from the body in the urine, and that the importance of their better-known function has quite overshadowed the presumably lesser, but nevertheless important work.

The Basis of Renal Medication.—Whether this function of the kidney is a result of an internal secretion or is due to other factors is not decided. As far back as 1869 Brown-Séquard held that the kidneys produced an internal secretion, and in 1892, with d'Arsonval,[1] he reported a series of experiments, which showed that the administration of renal extract postponed uræmic manifestations, and prolonged the lives of nephrectomized animals. Since that time numerous communications, especially from French writers, have substantiated this position.

Lépine[2] noted that the injection of the filtrate of a

watery extract of kidney produced a reaction with a rise of temperature and dyspnœa; while renal extracts evidently have an action different from that hypotensive property, supposed by Popielski to be inherent in all animal extracts. Their action is hypertensive, as Oliver and Schäfer[3] showed, for a cold, watery extract of fresh kidney, when injected intravenously in rabbits, soon produced a more or less marked increase in the tension.

Teissier,[4] applying the results of experimental physiology in therapeutics, found that the administration of a glycerin extract of kidney substance caused a diminution, and sometimes complete disappearance of certain serious symptoms, such as the dyspnœa, headache, and vomiting of severe kidney affections.

The Evidence against an Internal Secretory Function.—On the other hand, Biedl[5] states that "one thing is clear, however, and that is that these experiments supply no proof of a physiological internal secretion on the part of the kidneys."

Sajous is also opposed to the idea that the kidneys have an internal secretory function, and believes that the action of renal extracts is possibly due to the active principle of the adrenals. In an editorial article[6] entitled "Do the Kidneys produce an Internal Secretion?" the following evidence is brought forward: "In the light of recent data, however, these phenomena can as readily be attributed to physiological substances which normally form part of the renal tissues and fluids as to any supposititious internal secretion. As is well known, hypernephromata of the kidney are developed from adrenal rests in the renal substance, while the adrenal active principle is now known to be found in the blood throughout the entire organism, including, therefore, that of the kidneys. That an extract of the latter should contain

the adrenal principle is therefore self-evident. This fact being borne in mind, all the phenomena attributed to the so-called 'renal internal secretion' are found to coincide precisely with those awakened by the adrenal product. The elevated blood-pressure witnessed is a familiar effect of the latter. The rise of temperature was not only noted as a concomitant effect by Reichert, Lépine, and Morel, but Fuchs and Roth found recently that adrenaline increased markedly the intake of oxygen and the output of carbon dioxide. As to the dyspnœa and the ensuing arrest of respiration, obviously due to toxic spasm of the respiratory muscles, it has also been found to be a characteristic effect of adrenal extracts by Oliver and Schäfer, and more recently by Langlois and Garrelon. Even Brown-Séquard's observation, that renal extracts postponed the development of uræmia in nephrectomized animals and prolonged life, falls in presence of the fact, shown long ago by Langlois and developed by others since, that adrenal extracts are endowed with antitoxic activity—an essential feature in combating uræmia, itself due to retained poisons. Finally, Lewandowsky has shown that the effects ascribed to a supposed renal secretion could be obtained with venous blood derived from any other structure of the body. On the whole, the evidence is decidedly against the existence of a renal internal secretion, and it is hoped that the true status of other organs credited with such will soon be established. Then will it be possible to realize how truly important to the organism at large are the *bona fide* internal secretions."

The Therapeutic Value of Kidney Extracts.—While admitting the reasonableness of the above contention, there can be no denying the facts on record concerning the use of kidney preparations in the treatment of certain

conditions, and whether the therapeutic activity of such extracts is due to a hormone or not, the evidence is certainly in favour of the method, as will shortly be seen. The results published concerning the use of renal substance in therapeutics are already sufficiently extended, not only to authorize the employment of renal opotherapy in albuminuria, but also to establish its usefulness as an efficacious adjunct in a number of other disorders of the kidney.

The literature on the action of kidney extract in chronic nephritis is still very limited. Many divergent views are held by most authors, some claiming a complete cure following its use, while others disclaim any benefit whatever, and even warn against its use.

It is the opinion of several French writers that the favourable results of kidney extract may be looked for in uncomplicated cases of nephritis. When cardiac complications have arisen, this treatment is not so likely to be effectual. Subcutaneous injections are not without danger, probably owing to the fact that the extract is easily decomposed. Unquestionably a number of the unfavourable results reported are due to this cause. It is certain that a properly prepared extract, when given by mouth, presents no danger whatever.

Rénaut[7] of Lyons has added much to our knowledge of this subject, and, inspired by the same fundamental facts outlined by Brown-Séquard and others, uses and recommends the use of macerations of the fresh pulp of kidneys. He concludes that it constitutes one of the most active and effective means of treating conditions associated with renal insufficiency. He stated that it was better than any means then (1903) known, for it opens up the kidney incapacitated by the œdema of uræmia. It causes a rapid diuresis, and, when given over a suffi-

ciently long period, brings the amount of urine to the normal without harm to the glomerular structure. Rénaut continues: "This method has the advantage over others in that it reduces in a decided manner the albumin passed by the defective kidneys, at the same time frequently restoring their full activity. It can, therefore, be used to favour the restoration of the epithelia, which, in numerous cases, is histologically possible. No other form of treatment applied in nephritis has been known to do this." It also possesses another advantage—namely, its antitoxic action. Dubois[8] states that the antitoxin is derived from the products of the glandular epithelial cells of the convoluted tubules, and that this substance is not destroyed by its passage through the intestinal tract. When introduced into the organism by the mouth, it effects a true disintoxication. However, it has a somewhat cumulative action, and after twelve to fourteen days may cause pruritus and urticaria, with some slight gastro-intestinal disturbances. With that exception no ill-effects have ever been observed. The favourable results are regular, constant, and progressive, and the arterial hypertension, with a tendency to passive terminal dilatation of the heart, so frequently observed in interstitial nephritis, seems to be prevented.

Disadvantages of Fresh Preparations.—Several writers, notably Castaigne,[9] find that fresh kidney substance is not well borne when given *per os*, and therefore it has been given *per rectum*. When given by the rectal route, one-half to one fresh kidney is chopped fine, and water is added. This should be divided into three enemata of 200 c.c. each, and should be given through a high rectal tube after previous cleansing enemata.

Gilbert[10] does not recommend the fresh preparations, for he has found, in a series of experiments, that they

usually contain toxic substances in addition to those which are of therapeutic value. These toxins in certain cases may be neutralized and eliminated, and the value of this medication may be very evident; while, again, the capacity to destroy the harmful substances may not be present, and thus an already serious toxæmia may be added to. Again, disease may be present in the kidneys which are to be used, and this consideration militates against Rénaut's method.

To obviate the inconvenience of this rather unpleasant method of administration, active vacuum-dried extracts are now used in the form of powder, cachets, or tablets, although it is still insisted by a few writers that fresh preparations are more desirable. Such preparations are in comparatively frequent use, and in many cases of kidney disease render really effective service.

The Reduction of Albuminuria.—Besides the detoxicating influence already mentioned, and that which is frequently manifest in uræmia and other evidences of renal insufficiency, renal medication has other therapeutic virtues. Perhaps the most remarkable influence of this form of treatment is the reduction, sometimes in a very large degree, of albuminuria. It seems to indicate that extracts of kidney substance have the power to influence the passage of albumin through the kidneys. In the attempts which have been made to explain this action, several possibilities have been considered. Some think that these preparations play an antagonistic and neutralizing part, as poisonous substances undoubtedly are factors in the production of the disorders in question. In the opinion of Hallion[11] the general fundamental influence of opotherapy is in evidence here—viz., extracts of an organ act especially by stimulating the activity and regeneration of the corresponding cells which are disturbed.

Renal Insufficiency and Uræmia.—Under the influence of this medication one frequently notes the diminution or complete control of certain uræmic symptoms. One of the most troublesome of these, insomnia, is favourably influenced. Often œdema is reduced very rapidly, and at the same time the amount of urine is increased, and its low solid content is raised.

Capitan[12] reported a striking cure in a case of uræmia. The numerous and severe complications make the results obtained the more remarkable. An old man with a double aortic and mitral lesion, œdema of the lungs and limbs, ascites, dysuria, Cheyne Stokes breathing with very severe dyspnœic crises, and continuous delirium was given an injection of 3 c.c. of a hypodermic kidney extract (*néphrine*). At this time he was passing 300 c.c. of urine in twenty-four hours, and was supposed to be moribund. Several hours later an improvement was seen, and the total amount of urine the day after treatment was 850 c.c. No other medication was given. The injections were made daily, and two hours after the second dose 800 c.c. of urine were passed, the symptoms were subsiding, and the total urine on the third day amounted to 1,500 c.c. Injections were continued for a week, and all the symptoms, though, of course, not the heart lesions (which, however, eventually became well compensated), disappeared, and the patient was able to return to his business.

Roque and Lemoine[13] have had similar experiences. They find that a week or ten days of this treatment is usually sufficient. Within forty-eight hours of the first injection the acute phenomena of renal insufficiency begin to subside, with a marked increase in the urinary quantity and total solids.

Pulmonary congestion and the bronchitic disturbances

so commonly associated with certain forms of albuminuria are reported to have been ameliorated in consequence, doubtless, of an influence upon the circulatory disturbances, which at the same time are benefited. This is evidenced especially by the favourable changes in both pulse and tension. In addition to this, under the influence of renal opotherapy, digestive disorders, associated with renal insufficiency, mend encouragingly.

Vialard has used renal opotherapy in the treatment of what the French term "*imperméabilité rénale*," and has made two important communications to the Paris *Société de Thérapeutique*. In the second[14] he offers the following conclusions:

1. In cases of chronic nephritis a course of opotherapy, repeated several times, has caused a complete cure; but such cases are exceptional.

2. In the majority of cases of nephritis, renal opotherapy stops or lessens the crises of acute renal insufficiency, causing temporary disappearance of albuminuria, and of the signs of Bright's disease. It is to uræmia what digitalis is to asystole.

3. But in every case it acts only after causing abundant diuresis. This diuretic effect is almost always observed when the kidneys are not completely destroyed, and are able to react. If opotherapy is not a regenerator of the renal cellule, it is at least a powerful stimulant and a good diuretic.

Treatment with Serum from the Renal Vein.—Teissier and several other authors have given injections of serum obtained from the renal vein. The first application in man was made in 1897 by Turbure of Bucarest. In 1898 Teissier injected a serum in a young man suffering from very severe scarlatinal nephritis, and he was cured. Hypodermic injections into the abdominal wall of 20 c.c.

of the serum are given daily. This method has given very good results, but is rarely used on account of the difficulty in obtaining the serum.

Kidney Substance an Adjunct Remedy.—It goes without saying that renal opotherapy, in spite of the value which has been attributed to it, must be considered only as an adjunct method of treatment, save in exceptional instances. That the advantages are not due to the orthodox methods of treatment is clearly proved by considerable gains which have followed its addition to other procedures which have been in use for weeks or months. It is also well to remember that disturbances of the kind under discussion are serious, progressive, and quite often fatal, and that to expect too much of any method of treatment is unreasonable. However, one cannot overlook the advantages which have been recorded, and since the addition of this form of medication to the régime of nephritis is not accompanied by serious or inconvenient consequences, it seems on that account deserving of more extended application.

It is also well to mention that renal opotherapy is frequently combined with other animal extracts, and especially with preparations of liver, since, for obvious reasons, hepatic insufficiency is a predominating factor in many cases of renal disease.

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CHAPTER XVII

ARE THE TONSILS ENDOCRINOUS ORGANS?

The Anatomy of the Tonsils—Ott's Experiments—A Powerful Diuretic Principle—Influence on the Circulation.

THE function of the tonsils is not definitely known, and they are usually considered as a pair of more or less superfluous lymph nodes, whose value to the organism is considerably overbalanced by the facility with which they become infected and cause trouble.

The Anatomy of the Tonsils is well known, and frequent opportunity is had to study them both *in situ* and after excision. It is supposed by many that since the tonsils are composed mainly of lymphoid tissue, they serve to supply phagocytes to the mouth and pharynx wherewith to combat the bacteria entering the mouth. If this is so, it is easy to understand why they are so readily overcome and rendered useless; and one might be tempted to wonder why these organs, in the passage of generations, have not been modified by circumstances, and hypertrophied sufficiently to serve their presumed purpose usefully.

Many surgeons and general practitioners still appear to consider that the principal service of these bodies, like that of the ovary in times now happily past, is by their presence, so that their removal may furnish a convenient and remunerative addition to the day's work.

Ott's Experiments.—The possibility that the tonsils are internal secretory organs has only recently been considered, and it is to Ott[1] of Philadelphia that credit is due for considering this question.

Experiments were made with powdered dried tonsils of the calf and watery extracts of the same. The effect of these extracts was marked on the circulation and urinary secretion, while they caused a slight increase in the contractility of involuntary muscle, as noted in experiments with the intestines, bladder, and uterus.

A Powerful Diuretic Principle.—The most remarkable effect of injections of tonsil extract was on diuresis. An infusion of 0·13 gramme was injected in divided doses into cats, and an increase was recorded in the urinary secretion of over thirty times the original amount. As with extracts of the infundibulum, parathyroids, and pineal body, tonsil extract temporarily increases the volume of the kidney, and acts directly upon the cells of the renal tubules for some time after the vaso-dilatation has subsided, showing that the sum total of its action is not limited to the action attributed by Popielski to the theoretical "vasodilatin," which he states is to be found in extracts of all the various glands.

Ott[2] states that tonsil extract "seems to be a stronger diuretic agent than either infundibulum, parathyroid, or the pineal gland. In fact, it is the most powerful of all the internal secretions."

Influence on the Circulation.—Small or large doses cause a brief fall of blood-pressure and a decrease of the number of heart-beats. A reaction follows, during which the tension and pulse are increased. Large doses cause sudden arrest of the heart, and the authors infer that tonsil extracts act upon the heart muscle itself.

It is evident that the tonsil must be considered as more

than a lymphoid node, and that the above experiments prove that it contains certain substances closely resembling, if not actually, internal secretions.

Whether the hypothetical tonsil-hormone is of importance in the normal economy, and whether the removal of the tonsils may be the cause of the remote harm, one cannot yet say. It is quite possible that future investigations may throw light on this, and it is not improbable that our increased knowledge on the subject may give us a new organotherapeutic preparation.

At present, however, tonsil extracts are used only in the laboratories of a very limited number of enthusiastic delvers into the mysteries of the endocrinous organs.

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CHAPTER XVIII

THE CHROMAFFIN SYSTEM—ADRENAL THERAPY

The Components of the Chromaffin System—The Adrenals and their Active Principles—The Physiological Action of the Chromaffin Hormone—The Action of the Adrenal Cortex—The Relation of the Adrenals to the Gonads—The Action on Nutrition and Sugar Combustion—The Adrenals and Muscular Work—The General Indications of Adrenal Therapy—Hypoadrenia or Hypoepinephrinia — Hypoadrenia in the Acute Infections—The Adrenal Treatment of Typhoid—Adrenal Therapy in Asiatic Cholera—The Vomiting of Pregnancy—Cyclic Vomiting in Children—Chronic Hypoadrenia in Children—The Stimulation of Bone Growth and Nutrition—Adrenal Medication in Pulmonary Disorders—The Combination of Adrenal and other Endocrinous Preparations—The Influence of Adrenaline on Urticaria—The Adrenal Principle as an Angiotonic Remedy—The Treatment of Snake Bite—The Method of Causing Local Vaso-Constriction—The Control of Local Hæmorrhage—Adrenalin as a Rational Treatment of Asthma—Adrenal Extracts in the Salvarsan Treatment—The Relation of the Mind to Adrenal Activity—Chemistry and Nomenclature—Contra-Indications to Adrenal Therapy.

The Components of the Chromaffin System consist of a number of rather widely scattered cell aggregates, chief among which are the adrenal bodies or suprarenal capsules of Eustachius (discovered by this great anatomist between 1550 and 1560). These organs are classed as "the chromaffin system," because they contain certain substances which stain a characteristic yellowish-brown colour by chromium salts. This staining capacity was first noticed by Henle (1865), and in 1890 Stilling applied the term "chromophil," which is still used by some writers. The

term "chromaffin" was introduced by Kohn in 1898. The units composing this series of organs have also been given the name "paraganglion."

As far as is known at present, all chromaffin tissue is considered to be very similar to the chromium-staining tissue of the adrenals, and many insist that the chromaffin organs other than the adrenals themselves are virtually accessory adrenal glands; at least, it has been shown that the extracts of these organs have practically the same action as extracts of the adrenal medulla.

The chromaffin system, then, includes the intercarotid body, or carotid gland of Luschka, Zuckerkandl's aortic paraganglion in the fœtus, the accessory adrenals or interrenal bodies, and the medullary substance of both the adrenal glands. The anterior lobe of the pituitary body also contains many cells which give the same characteristic staining reaction.

There is a close relationship between the chromaffin system and the sympathetic nervous system, and several writers have connected them, and it is for this reason that this chapter has been included in the section dealing with the "Nervous System."

The coccygeal body has for some time been considered a part of the chromaffin system, although it does not manifest all the characteristic staining reactions. Biedl denies that it belongs to the sympathetic system.

The Adrenals and their Active Principle.—Concerning the action of the internal secretion of the adrenals we have accumulated a great deal of information in the past fifteen years—much more than can be condensed into this chapter. It must still be admitted, however, that we cannot yet satisfactorily explain the whole of the activities of these peculiar bodies, which, it is now known, are constantly yielding to the blood a chemical agent, or hormone,

which stimulates the contractions of the heart and arteries, and assists in the promotion of every action dependent upon the sympathetic nervous system (Langley).

The best recent reviews of this subject are to be found in Lucien and Parisot's book, chapter xi. of Swale Vincent's book, and Biedl's second German edition.* Naturally the majority of the pages of these books are concerned with general considerations, for which we have little space here, while the therapeutic phase of the subject is incidental. An attempt will be made to concentrate here the gist of our present knowledge of the administration of adrenal preparations in general and special practice.

Three points brought out in the introduction to Vincent's[1] monograph may well be reiterated here; and it seems advisable to quote his statements *in extenso:* "There are two important discoveries which stand out among all others as epoch-making. The first is the observation by Addison in 1849, that certain cases of disease characterized by pigmentation of the skin, languor, and other symptoms, are associated with destructive lesions—usually tuberculous—of the adrenal bodies. The second is the discovery in 1894 by Oliver and Schäfer of the blood-pressure-raising activity of extracts of the medullary portion of the gland. We are, however, by no means clear, as will be seen in the sequel, what is the precise relationship between the facts revealed in these two discoveries. A third very important step in our progress ought to be referred to in this place. This is the isolation in crystalline form of the active principle of the medulla of the gland (*i.e.*, of the chromaphil tissues) by Takamine and Aldrich independently."

The Physiological Action of the Chromaffin Hormone.—The activity of this active principle of the adrenal medulla

* See the "List of Books" in Chapter XXXVII. of the Appendix.

(*adrenalin*) is very great, extremely minute doses sufficing to cause marked physiological responses. The principal influence is upon the musculature of the vascular system, a fact which is responsible for the two factors which have made the discovery of this substance so eminently useful—*i.e.*, (1) constriction of the arterioles and capillaries due to the excitation of the peripheral nerve endings and quite apart from other nerve influences, since the constricting action continues in spite of section of the medulla or paralysis of the vasomotor centre; and (2) direct stimulation of the heart muscle. As a result of this the two main therapeutic indications are made evident: (1) The control of local hæmorrhage, and (2) the raising of blood-pressure. This will be referred to more fully farther on.

The Action of the Adrenal Cortex.—The adrenals, like the pituitary and ovaries, are supposed to have a double function, and histologically they are found to be composed of two distinct forms of cells—the cortex and medulla. In certain fish these two parts are completely separated, and comparative anatomy has shown us that developmentally the adrenal bodies represent two distinct sets of organs which in the higher vertebrates are fused. It is the medullary portion which is used in the preparation of the angiotonic substances used in therapeutics, and their activity corresponds to that of the adrenal or chromaffin hormone. The cortical cells evidently also have an internal secretory function, and, according to Bérnard,[2] their presumed hormone has the power to neutralize the poisonous substances produced during muscular activity. It is concluded that the myotonic action of the adrenals is due to the activity of the cortex, while the angiotonic action is caused by the medulla.

The presence of a myotonic internal secretion in the adrenal cortex may account for the tonic and anti-

asthenic action of extracts made from the whole gland. This may also be a good explanation of the vogue of the several excellent powdered total extracts (tablets or cachets) which are commonly used in France. The general tonic results, other than those due to adrenaline, are frequently used in the hypoadrenia of children and the acute infectious diseases, as outlined later.

The Relation of the Adrenals to the Gonads.—There is a more or less intimate connection between the adrenals and the ovaries. A remarkable fact emphasizing this is brought forward by Bulloch and Sequeira,[3] who have shown from the study of pathological phenomena that the adrenal cortex is largely responsible for the development of the secondary sex characteristics.

As we have seen, the adrenal cortex and medulla have a different development and different functions; according to Glynn[4] the former is especially connected with growth and sex characters, the latter with blood-pressure. The enlargement of the adrenal cortex during breeding, during pregnancy, and after castration, and the small size in deficient sexual development, are additional exidence of the association of the cortex with sex characters.[5] Glynn continues: "Adrenal hypernephromata are associated with sex abnormalities almost invariably in children, usually in adult females after the menopause, or in adult males. Hyperplasia and hypernephromata of the adrenal cortex in females are usually associated with a diminution of certain female, and a development of male, sex characters. The converse rarely occurs. The functional association of the adrenal with the pituitary and other ductless glands, and the appearance of certain sex abnormalities in acromegaly and pineal tumours, indicate that a true solution of the connection between the adrenal cortex and sex will only be found when the inter-relation-

ships of the various ductless glands are better understood."

The adrenal medulla is also intimately connected with the ovaries. Keller[6] suggests that the ovaries have an inhibitory action on the adrenal internal secretion. After castration he found that the glycosuric action of the chromaffin hormone was markedly increased. The absence of the ovaries causes an increased functional activity of the chromaffin system with the well-known climacteric symptoms—increased blood-pressure, flashes of heat, dizziness, headache, etc.—which are identical with the manifestations of hyperadrenia. Varaldo[7] demonstrates this relationship in another way. He injected epinephrin into a series of rabbits. During pregnancy epinephrin-poisoning was increased, but was diminished by castration. Repeated injections caused an obvious decrease in the size of the ovaries with degenerative changes in which the glandular structures were replaced by connective tissue.

In Chapter XXIV. further evidence is given to show that there is a relation between the adrenals and the ovaries, and that therapeutic advantage may be gained from the application of the knowledge.

The Action on Nutrition and Sugar Combustion.—The chromaffin hormone appears to exert an important action upon the phenomena of nutrition, but it is difficult to augment our knowledge of the limits of its activities because of the toxic effects produced, chief among which is glycosuria.

In 1901 Blum[8] made the notable discovery that glycosuria is produced in certain animals following the hypodermic injection of adrenaline. This has since been considerably amplified by Zuelzer[9] and his co-workers. This fact must be remembered when one is tempted to use

adrenal preparations in diabetes mellitus, for patients suffering with pancreatic diabetes, being already in a state of hyperadrenia because of the lack of the pancreatic hormone, are extremely sensitive to all adrenal preparations. The relation of the hormone balance to glycosuria is more thoroughly considered in Chapter III., and also in the chapter on the pancreas (Chapter VII.).

The Adrenals and the Muscular Work.—Langlois was the first to show that the adrenals are an important factor in the destruction of muscle poisons; and Dieulafoy noted the connection between asthenia and certain pathological adrenal states. The fact that one of the prominent symptoms of Addison's disease is severe muscular asthenia, has led many to believe that muscular efficiency is dependent upon the adrenal secretion. Other experimental proof has been brought forward to establish the association of these factors. Experimentally it has been shown that partial or complete ablation of the suprarenal capsules reduces the muscular power, and injections of extracts of these glands have a stimulating effect.

"Cannon and Nice[10] have attempted to unravel the relations of the adrenals to the muscular functions. There can be no question, from the evidence now available, that there is a marked improvement in muscular contraction after adrenal secretion is evoked or after epinephrin* is injected. A large part of this increased efficiency is unquestionably due to the improved circulation . . . and fatigued muscles may thus be prepared by the secretion of the adrenal glands for better response to the demands of powerful nervous discharges."[11]

The General Indications of Adrenal Therapy.—The value of preparations of these glands is well known, and they are in general use to-day. Many thousands of articles and

* Note the paragraph, "Chemistry and Nomenclature," on p. 282.

clinical reports concerning their uses are scattered throughout the world's medical literature. These are, for the most part, devoted to their styptic or pressor value. Adrenal preparations have a wider range of usefulness than is ordinarily supposed.

The conditions in which this form of medication is of value may be divided into two classes: (1) Adrenal insufficiency or hypoadrenia, in which there is a definite pathologic lack of the chromaffin hormone, the chief among which are Addison's disease, adrenal tumours with consequent disturbed secretory function, certain acute infectious diseases, during which a hypoadrenia develops (*e.g.*, diphtheria, cholera, scarlet fever, typhoid fever), and certain nutritional disorders, especially osteomalacia, rickets, etc. (2) Those conditions in which the vaso-constrictive, myotonic or diuretic properties of adrenaline are available — its empiric application as a remedy.*

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 Béclère[12] obtained a complete and permanent cure

* This is strictly the case, although the author is frank to state that the classification as "empiric" of the application of the vaso-contractor action of adrenaline has been criticized. As a matter of fact, the word "empiric" comes from the Greek ἐμπειρικός, experimental, and is used to classify those methods of treatment that are based on experience. With this definition in in mind, the author's position will be clear. There is no particular lack of the adrenal hormone in, say, conjunctivitis ; but the application of what we have learned from experience, as regards the local vaso-constrictor action of this substance, indicates that it would likely be useful in reducing the local congestion in the conjunctiva ; and clinical results have established the indubitable value of this empiric application.

in one case. He credits the treatment with causing a compensatory hypertrophy of the unaffected areas of adrenal tissue. The dosage in Addison's disease is necessarily greater than ordinarily would be the case. Two or three grains of desiccated adrenal substance should be given three times a day.

Hypoadrenia or Hypoepinephrinia.—The disorders of the adrenals accompanied by anatomic changes are fortunately not very common, while functional hypoadrenia (sometimes termed "hypoepinephrinia"), varying very greatly in degree and the consequent manifestations, is of frequent occurrence. In general, the evidences of the presence of such conditions are 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.

Many of the theories, for which he was roundly criticized, advanced by Sajous in his monumental work,[13] are now established facts, and as such form the basis of a therapeutic procedure of proved utility. The prominence which this writer has given to the activities of the adrenal system* is none too great, for undoubtedly the part that the adrenals play in the essentially vital processes is as important as it is complex. Attention is again called to the reference made to Crile's[14] theory (see p. 38) and remarks regarding the "kinetic system," and by comparing the statements in this chapter with those in Chapter III., it will be evident that the "adrenal system"

* Fully 700 of the 1,800 pages of Sajous's "Internal Secretions and Principles of Medicine" are devoted to the part of the endocrinous system which he terms the "adrenal system." This, it should be remembered, consists of the thyroid apparatus, anterior pituitary, and the adrenals themselves.

of Sajous and the "kinetic system" of Crile are very nearly, if not quite, identical.

According to Bérnard,[2] the syndrome *hypoépinéphrie* is characterized by the presence of muscular asthenia and diminished arterial tension. The former, which is the chief manifestation, may be so intense as to simulate a veritable paralysis. The arterial hypotension may express itself in a number of ways; there may be tachycardia, arrhythmia, a tendency to collapse and syncope, and peripheral vasomotor disturbances. There is also an impairment of the digestive functions. The nervous manifestations include mydriasis, headache, delirium, convulsive or apoplectiform states, coma, and sudden death. Sergent[15] has distinguished three different types of adrenal insufficiency—the chronic, the subacute, and the acute. The last of these, which has not been recognized until recently, may be revealed under the guise of an acute poisoning, a peritonitis, or a meningitis. Many of the manifestations of acute infections or toxic conditions are to be attributed to adrenal insufficiency. These manifestations are apt to occur particularly in diphtheria, scarlet fever, typhoid fever, erysipelas, and chloroform-poisoning.

Hypoadrenia in the Acute Infections.—Numerous other authors have drawn attention to the fact that there is a connection between several of the more severe acute infectious diseases and acute toxic hypoadrenia. The adrenal insufficiency thus brought about may complicate matters very seriously, and it has been proved by numerous autopsies that the adrenals are not infrequently the seat of hæmorrhages. The serious toxæmias of such fevers are often the cause of an adrenal disturbance producing a decrease in the normal supply of the all-essential internal secretion, which results in a con-

siderable reduction in blood-pressure, myasthenia, and a tendency to collapse. Netter has done much to impress the importance of this, and records many cases in which benefit followed adrenal therapy. Several French writers recommend a dosage of ¼ to 1 milligramme of adrenaline, according to the conditions present. Where circumstances warrant its use, the application of adrenal therapy quickly results in an increase of strength and reactive powers, and, of course, the tension is raised and the heart strengthened.

The Adrenal Treatment of Typhoid.—In a paper on the relation of hypoadrenia to typhoid fever, read before the French Académie de Médecine, Sergent connects certain conditions which may supervene in typhoid fever with the syndrome of adrenal insufficiency. This is in harmony with this investigator's previous efforts to prove that adrenal insufficiency may be observed in all infectious diseases as well as in all severe intoxications. Sergent's theory is of great practical importance, as it involves the use of adrenal medication in such cases. Adrenal insufficiency may be suspected in an infectious disease when agitation, excitement, and fever give place abruptly to prostration, lower temperature, and arterial hypotension, with the white adrenal line* and a tendency to collapse. The not infrequent complete prostration and small pulse found in typhoid are signs of adrenal insufficiency. These symptoms attain their maximum in certain severe typhoid cases, even simulating peritonitis or internal hæmorrhage, and disappear rapidly under adrenal therapy. Certain complications of con-

* This is a dermographic sign consisting of a white line upon the skin of the abdomen, which follows light pencilling with the finger, and which remains much longer than usual, sometimes two or three minutes. This *ligne blanche surrénale* is considered by Sergent to be a characteristic sign of hypoadrenia.

valescence, such as prostration, anæmia, psychasthenia, etc., are also due to deficient adrenal activity from subacute inflammation of the adrenals. From the data which he has so carefully gathered, Sergent concludes that the systematic employment of adrenal preparations is justified in all cases of typhoid, and that the extracts of the entire gland are indicated for the severe complications due to acute hypoadrenia. Except in those hypertoxic or hæmorrhagic cases which defy all treatment, this method, associated with the ordinary treatment of typhoid, gives considerably better results.

One of the outstanding features of dengue fever is the profound asthenia, and only recently it has been shown that this symptom (as well as the lumbar pain, cramps, vomiting, etc.) is amenable to adrenal medication. This fact, accidentally discovered, has led to an investigation of the relation of adrenal insufficiency to dengue fever, and it seems clear that this is a constant and essential factor in this, to most physicians, rather rare disorder. Khoury[16] relates having seen rapid improvement follow the administration by mouth of 30 minims (2 c.c.) of adrenaline solution (1 in 1,000), and urges its use in every case.

Sajous[17] describes a form of adrenal insufficiency occurring late in the course of a febrile disease, which he considers a result of exhaustion of the adrenals due to their effort to protect the organism. He designates this condition "terminal hypoadrenia," and suggests administering dried adrenal gland in 3-grain (0·2 gramme) capsules three times a day, the dose being gradually increased to 5 grains (0·3 gramme). In more dangerous cases *adrenalin* may be injected intravenously in saline solution, or the solution (1 in 1,000) may be given subcutaneously in 10-minim doses.

Adrenal Therapy in Asiatic Cholera.—It seems that the most useful drug in the treatment of cholera is adrenaline. This does not mean that the use of vaccines, sera, or other drugs is supplanted, but rather supplemented. Sajous in 1903 first pointed to a connection between adrenal insufficiency and Asiatic cholera, and since then several interesting clinical reports have appeared.

Naamé[18] of Tunis has reported the favourable results of this treatment during an epidemic of cholera. He finds that doses of 1 to 2 milligrammes of adrenaline (not the total extract, for it is suggested that the cortical part of the gland has a detrimental action in this particular condition) given hypodermically, or preferably intravenously with normal saline solution, stop the rice-water stools, stimulate the heart, raise the pressure, and in many cases cure the disease. Naamé writes: "I am firmly convinced that the cholera syndrome is an acute hypoadrenia due to poisoning of the adrenals by toxins of the cholera spirillum. . . . The attack consists of two phases—the first bacillary, or intestinal, comparatively harmless; the second toxic, or adrenal, frequently fatal. The great tolerance to adrenaline manifested by cholera patients shows that the organism is appropriating an active principle of which it has been deprived by the disease."[11]

A number of other reports from India and elsewhere confirm this position, and it seems established that adrenal preparations are always indicated as a part of the treatment of Asiatic cholera, plague, and similar seriously toxic infections.

The Vomiting of Pregnancy.—Sergent and Lian[19] think that the adrenals are a means of defence in the control of the toxæmias of pregnancy arising from the chorionic villi. They noted that where this toxæmia is

unusually marked, the adrenals may become rapidly exhausted through overwork. They therefore treated refractory vomiting with adrenal extracts, and record several cases in which prompt results were secured from cachets containing 5 grains (0·3 gramme) of extract given two or three times a day.

Silvestri,[20] as well as other Italian investigators, is quite partial to this method of treatment. He administers adrenaline internally. He noticed that severe vomiting often occurs in cases of Addison's disease, as also in animals from which the adrenals had been removed. In the case of a woman in whom the vomiting had resisted all forms of treatment, adrenaline caused a complete cessation in two days. Zanfrognini and Rebaudi also report successful treatment. The latter describes the case of a young woman in the third month of her second pregnancy who was so exhausted that abortion had been decided upon. Adrenaline was, however, first tried, 10 drops of a 1 in 1,000 solution being given twice daily. The effect of the treatment was so rapid that in about a fortnight the dose was reduced to half. In another ten days the vomiting was entirely controlled, and remained so until term.

Silvestri,[21] in a more recent reference to his use of this method in pregnant women, does not agree with those writers who emphasize the harmlessness of this treatment in the dosage advised. Two recent experiences tend to contradict this assumption. Two women in the second month of pregnancy were given a mild course of adrenaline and calcium salts, on account of an incipient apical process and defective nutrition. Each aborted in less than a month. He has given this treatment to other women in later months of pregnancy, and never before witnessed any tendency to abortion; and one of the

present patients had taken it without disturbance during the last three months of a preceding pregnancy.

Cyclic Vomiting in Children.—This condition, occasionally called "acetonæmic vomiting," because of the frequency with which it is associated with acetonuria, is considered by Terrien and others to be due to a transient hypoadrenia. This being the case, the value of adrenal therapy will be obvious. Terrien reports three cases in detail in which rapid cessation or relief of the symptoms followed injections of adrenaline. This writer enumerates the signs of hypoadrenia very similarly to those already mentioned. They vary from simple lassitude to complete depression and somnolence; lumbo-abdominal pains, digestive disturbances varying from a comparatively unimportant hypotension to syncope and sudden death. These same symptoms are found in cyclic vomiting of children as well as in hyperemesis gravidarum and certain cases of typhoid fever. They have frequently yielded to the adrenal treatment, and this seems to be proof of the relation of hypoadrenia to the causation of these serious conditions.

Chronic Hypoadrenia in Children.—The disorders with which adrenal insufficiency has been associated in the preceding pages are for the most part acute or subacute conditions. Occasionally, however, a chronic hypoadrenia may be found.

D'Œlsnitz[22] called attention to this at the recent International Congress of Medicine (London, 1913). He points out that there may occur in childhood, either spontaneously or as a sequel to some acute disease, slightly marked but persistent disturbances, which at length react seriously on the general state and growth of the child, and which are due to partial insufficiency of the adrenal function. In very young children thus affected

development in weight and height is at a standstill, the muscles are flabby, walking is delayed, and the child is apathetic and at times somnolent. Adrenal therapy usually brings about more or less rapid cessation of these manifestations. In boys before puberty there is noted a condition of apathy, fatigue, and physical and mental indolence. The child grows thin, and the blood-pressure is low. Administration of adrenal preparations under these conditions renders the boy more alert, and leads him to work better and suffer less fatigue; the blood-pressure rises, and the body-weight and stature augment in a few months. Manifestations such as those described may, of course, be due to other conditions, but the benefit accruing from adrenal therapy in many cases would seem to indicate a specific deficiency on the part of the corresponding organs.

Usually the hypoadrenia is associated with deficient internal secretory activity on the part of certain of the other ductless glands. This hypoendocrinism is more fully dealt with in the consideration of the use of pluri-glandular extracts (Chapter XXX.).

The Stimulation of Bone Growth and Nutrition.—The adrenals are evidently concerned in the growth and maintenance of the osseous system. Carnot and Slavu[23] seem to have demonstrated this most conclusively. In order to ascertain the action of adrenaline in osseous repair, they detached from the tibia a small ring of bone and replaced it in position. Certain of the animals experimented on were treated daily with injections of adrenal extract in doses of 0·006 gramme; others served as controls, and received no injections. It was found that osseous repair was further advanced on the eighteenth day in the treated animals than it was in the controls on the twenty-third day.

In this connection it is interesting to note that Carnot[23] has reported good results from this adjunct method of treating fractures, and its value is increased where the fractures are slow in uniting.

Numerous observations have confirmed the value of adrenal extracts in osteomalacia, although it is evident from a few contradictory reports that its value is not constant. In spite of much clinical and experimental research, it is still difficult to say to what factors the beneficial effects of adrenal therapy are due. It may result from a direct influence upon the calcium metabolism; or, again, it may be brought about by the action of the adrenal hormones on the other endocrinous glands, stimulating some or antagonizing others. Probably Blair Bell is the nearest to the solution of this question in his ideas regarding the control of calcium metabolism by the ovaries, and the favourable action of adrenal preparations is due in part to their reflex (humoral) action upon these glands.

Blair Bell[24] states that: "The administration of suprarenin has been successfully employed for osteomalacia. This may be not only because suprarenin is antagonistic to the ovarian secretion, but also because in this disease there may be suprarenal insufficiency, a supposition which is supported by the fact that in one case in which I produced experimentally suprarenal insufficiency in a rabbit, the bones of the fore-legs became bowed. Further, in most of the animals operated on there was an enormous increase in the urinary excretion of calcium. It appears, therefore, that the secretions of the suprarenals are of great importance during pregnancy in assisting the absorption and retention of lime." A valuable résumé on this subject is found in the communication of Bonnamour and Badolle.[25]

Adrenal Medication in Pulmonary Disorders.—Sergent[26] is partial to adrenal therapy in certain cases of tuberculosis. In many sufferers from this disease will be found a hypoadrenia which manifests itself by symptoms of asthenia out of proportion to the pulmonary lesion. Occasionally there may be a pigmentation of the skin or mucous surfaces. Then, too, there are cases of phthisis in which a tendency to collapse is prominent, or in which the heart itself is evidently especially weak; and, finally, the favourable influence of the adrenals upon calcification renders such medication of still broader service.

Hence the administration of dry adrenal extracts or *adrenalin* often may be followed by encouraging progress in the control of a tubercle infection. Sergent especially recommends an extract of the whole gland—cortex and medulla—in the asthenic cases.

Adrenaline has been used with very good results in pleurisy. Wedensky[27] mentions a series of twenty cases in which intrapleural injections of a 1 in 1,000 solution of epinephrine hydrochloride constantly yielded such favourable results that he has discarded all other methods of treating this condition, except by surgical intervention where indicated. The amount injected was at first 0·3 c.c. (5 minims), and on the four or five succeeding days 0·2 c.c. (3·33 minims), in saline solution. As a result, the temperature begins to descend on the third day, and the effusion is rapidly absorbed, so that by the tenth day the presence of fluid was difficult to demonstrate. In dry and in purulent pleurisy this treatment was employed with benefit. Distinct improvement in the general condition was among the additional favourable effects noted.

The same procedure was tried by Volkova in six

cases of pleurisy with effusion, all in children ranging from two to ten years of age. The dose used was at first 0·15 c.c. (2·5 minims) of the solution; this was later increased to 0·3 c.c. (5 minims), and in one case even to 0·5 c.c. (8 minims). Rapid absorption of the effusion followed, even in cases where previous exploratory puncture had shown little or no tendency to initiate absorption.

The Combination of Adrenal and Other Endocrinous Preparations.—Adrenal extracts are almost invariably given alone, but there are a few references in the literature to its administration in combination with pituitary preparations.

Houssay[28] says that the combination of *adrenalin* and *hypophysin* unites the extensive adrenaline action upon the heart and bloodvessels with the protracted effect of *hypophysin* upon these organs. When these two substances are properly mixed, the depressive action of the pituitary extract is lessened. Four to five drops of a 1 in 1,000 solution of *adrenalin*, with 1 c.c. of the "active constituents of hypophysis," or of a 20 per cent. dilution of some of the other constituents of the posterior lobe, may be given intravenously in cases of shock or collapse. Houssay believes that, as *adrenalin* is rather toxic and *hypophysin* is comparatively harmless, it is possible to reduce the dose of *adrenalin* by this combination, and yet increase its beneficial action. The combination may be used successfully in fulminating intoxications associated with hypotension, in tachycardia, and in myocarditis toxica, either subcutaneously or by 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 hypo-

physis counteracts the mydriatic effect of the adrenal extract.

Weiss[29] recommends, in the treatment of asthma, a preparation of adrenal and pituitary extracts known as *asthmolysin*, and believes that in many cases asthma is of humoral origin, and due to disturbance in the balance of the internal secretions. Other combinations have been suggested, and several of them are mentioned in Chapter XXX.

The Influence of Adrenaline on Urticaria.—In six cases of urticaria which Swann[30] has treated by the subcutaneous administration of adrenaline, the injections were followed by a rapid disappearance of the erythema and wheals. In each case a dose corresponding to about 8 minims (1 in 1,000 solution) for an adult was given hypodermically, and the dose was repeated in ten minutes. Two doses sufficed in every instance to cause the complete fading of the rash. An improvement was usually seen about eight minutes after the initial dose, and was most marked between ten and twenty minutes, during which time, especially in the severe cases, the rapidity with which the eruption subsided was very striking. After twenty minutes there usually remained some erythematous blotches, or small pale wheals, which continued to fade until the skin looked entirely normal. All itching ceased in from five to twenty minutes after the first dose.

The Adrenal Principle as an Angiotonic Remedy.—We now must consider briefly the influence of certain preparations of the adrenal medulla in the treatment of circulatory conditions. Adrenal extracts produce an extraordinary hypertensive action due to the vaso-constrictive influence of the chromaffin hormone upon the peripheral vessels as well as upon the heart itself. This action

upon blood-pressure was, as we have already noted, first discovered by Oliver and Schäfer in 1894. This constitutes the principal therapeutic property of these preparations, and is the basis of almost nine-tenths of its application as a local hæmostatic—a matter which will be referred to again.

For several years adrenaline has been used with excellent results in the treatment of shock and collapse, but it is now almost entirely superseded by pituitary preparations, which have an equally salutary effect, and the additional advantage that the influence is not so ephemeral but persists for hours, where the action of the adrenal preparations lasts only for minutes.

Bernouilli,[31] referring to this, states that: "It is possible that pituitary preparations, the stimulating action of which is less dangerous and more lasting, will in the future replace adrenal preparations, to which will always remain the chief place in local anæsthesia and hæmostasis."

A number of writers have recommended adrenal extracts as a means of treating functional and organic diseases of the heart. Floersheim[32] calls it an ideal heart stimulant, and says that "no other drug can compare with it for rapidity of action, strength, efficiency, and safety combined." He reports a favourable influence upon arrhythmia, dilatation and the strength of the heart, but found no effect in those cases of organic cardiac disease in which the pulse was strong and regular.

In the opinion of the present author, every case in which adrenal preparations are used internally should have both pulse and blood-pressure recorded. Where this remedy is given for two or more days, charts should be carefully kept, so that the physician may be aware of the changing status of these manifestations.

The manufacturers of *adrenalin* have culled the literature and collated many valuable clinical reports[33] referring to the successful use of this preparation in over ninety different conditions, which fill a most interesting 104-page brochure. These experiences show the broad scope and unquestioned value of this remedy, especially in what has previously been called "the empiric use" of this substance.

The Treatment of Snake-Bite.—It has been shown that adrenaline has the property of retarding absorption from the tissues into the circulation. This, combined with its profound influence upon the circulation, has led to its use in the treatment of snake-bite. A number of reports may be found which show that it has been of great value in such cases. It would almost appear that there is an associated antitoxic action, as the following case reported by Lankford[34] seems to indicate: "A young man was brought from the country bitten by a large rattler snake, and was in a condition of profound prostration, with rapid and feeble heart action, pulse somewhat irregular, temperature 96° F., vomiting frequently, restless and delirious. I used *adrenalin* freely, and in a very short time was rewarded by a reaction. The pulse came down and grew stronger, blood-pressure rose, temperature came up to the normal and a little above, the vomiting ceased, and altogether the general condition was such within two hours that I could see that the first results of the poison were under control. This was quite remarkable to me in face of an extremely dangerous condition. Of course, there was the typical swelling and severe inflammation, but besides overcoming shock, the *adrenalin* seemed at once to arrest the poisonous action of the venom upon the organism at large."

The Method of causing Local Vaso-Constriction.—Scores of disorders in which local vaso-constriction is useful frequently respond to adrenal preparations when applied locally or given internally. As a local vaso-constrictor these have supplanted all other preparations and procedures. In nose and throat therapeutics and surgery it is daily used alone, or associated with cocaine, eucaine, novocaine, or other local anæsthetics. Such combinations are especially useful since less of the alkaloid is required on account of the anæsthesia produced by the local constriction of the vessels, while general absorption of the alkaloid is to a certain extent hindered. In local inflammations of the various mucous membranes it is of much value, and the local hyperæmia associated with such conditions as acute and chronic coryza, rhinitis, tonsillitis, pharyngitis, laryngitis, and hay fever respond to its action very readily.

The Control of Local Hæmorrhage.—In gastric and duodenal ulcer, when hæmorrhage had occurred, there are numerous reports of the good results of this treatment. Some writers have mentioned a reaction following the treatment, which it is desirable to avoid. It has also been used in typhoid fever to prevent further loss of blood, but it should be borne in mind that adrenaline is a two-edged sword.

Hæmorrhoids, especially those in which there is a continual slight hæmorrhage, may be treated by means of suppositories containing adrenal extracts. It is well to remember that a condition of turgescence has often been found to follow the temporary local anæmia caused by the adrenaline.

In genito-urinary practice adrenaline has been successfully used as a decongestive agent generally, and in urethritis, renal and ureteral hæmorrhage, cystitis and

cystic hæmorrhages, prostatic congestion (as a local application and in suppositories), and the reduction of paraphimosis.

In dentistry the various adrenal preparations are currently used alone or with local anæsthetics. Analgesia is facilitated, and the congestion of the inflamed areas diminished.

In the treatment of morphine addiction the circulatory disorders and collapse may be temporarily controlled by this method, and Reichert is encouraged by his successes with it.

Adrenalin as a Rational Treatment of Asthma.—The vaso-constricting action of the adrenal principle has made it a useful means of controlling the paroxysms of bronchial asthma. The mechanism of its action is now well understood, although this should strictly be considered an empiric method of treatment. A number of papers relate very good results following the administration of *adrenalin* by any of the usual methods—locally as a spray, by mouth, subcutaneously, or intravenously. A most interesting report was recently made by Meulengracht,[35] who considers *adrenalin* to be the most satisfactory means of treating asthma. He gives hypodermic injections of ½ c.c. (corresponding to 0·0005 gramme adrenaline chloride), and finds this method much more satisfactory than the local spray. It has no cumulative action, nor does the system become accustomed to the drug. A case is reported to whom Meulengracht gave no less than 1,500 such injections in nine months.

Adrenal Extracts in the Salvarsan Treatment.—It has been suggested by Milian[36] that the occasional accidents following the Ehrlich treatment of syphilis are in part due to a disturbance of the adrenal function. The symptoms of *salvarsan*-poisoning—vomiting, profuse

diarrhœa, cyanosis, anuria, etc.—are very similar to those of the choleriform type of acute adrenal insufficiency, and this writer is convinced from practical clinical experience that adrenaline injections may be used as a preventive of this condition. He also reports a case in which its curative effect was manifest in a moribund patient. The suggested dose is 1 to 1·5 milligrammes of *suprarenin*, injected into the muscles of the buttock. Ravaut confirms this, and tells of having observed the disappearance of the symptoms of nitrite-poisoning (*les crises nitritoïdes*) following injections of the adrenal principle. This new chapter in salvarsan therapy is of considerable importance, and further investigative work should be done.[37]

The Relation of the Mind to Adrenal Activity.—The broader influence of the chromaffin hormone in normal physiology, and possibly in therapeutic practice, will be better appreciated when the results of the most recent work on this subject are mentioned. It is fortunate that we are able to estimate very minute quantities of adrenaline; and instead of having to depend upon extirpation experiments, certain physiological phenomena may be brought about, and the resulting changes in the adrenaline-content of the blood accurately noted. Cannon[38] of Harvard has recently published some suggestive conclusions regarding an emergency function of the adrenal medulla. Fear, rage, or pain, causes an increased liberation of the internal secretion of these glands, and by its stimulation* bring about changes that are directly ser-

* The results of this stimulation are thus explained by Cannon: "The cessation of activities of the alimentary canal (thus freeing energy for other parts), the shifting of the blood from the less insistent abdominal viscera to the organs immediately essential to life itself, such as the lungs, the heart, the central nervous system, and, at critical moments, the skeletal muscles as well the increased cardiac vigour, the quick abolition of muscular fatigue, and the mobilizing of energy-giving sugar in the circulation."

viceable in making the organism more efficient in the struggle which may be in prospect.

Occasionally this stimulation may be too great, and the resulting condition of adrenal depletion may be serious. In this connection it may be interesting to recall that in Asiatic cholera the most distressing symptom is the terrible pain in the abdomen. Attention has been directed to the theory that cholera is always associated with acute adrenal insufficiency; and, with Cannon's conclusions in mind, it is not unreasonable to suppose that the pain itself is an important factor in causing the hypoadrenia. If this is so, the great indication is to obviate the pain as much as possible, at the same time attempting to replace the lost adrenal principle, and, of course, to control the infection.

Chemistry and Nomenclature.—The chromaffin hormone is one of the most active of all the internal secretions. It has been isolated in the form of a definite crystalline compound, having the formula $C_9H_{13}O_3N$ (Aldrich), and a very similar body has been prepared synthetically. There is a vast literature on this subject. Scores of preparations are upon the market, each with its different name, a fact which is at once inconvenient and unscientific. The Council of Pharmacy and Chemistry of the American Medical Association has suggested the word "epinephrin"* as being the most suitable, and the *Journal of the American Medical Association* now uses it exclusively, and reports work done with *adrenalin*, *hemisine*, or *suprarenin*, etc., with the "standard" word "epinephrin," which hardly seems fair to the reader or the manufacturer.

* This word "epinephrin" was given by Abel to what he supposed to be the active principle of the adrenal gland, but which was found later to be a mono-benzoyl derivative of the active principle. Later Abel retained this name, and it has been employed as a synonym for *adrenalin* and other similar, *but different*, preparations.

Contra-Indications to Adrenal Therapy.—One of the principal contra-indications of the administration of all adrenal preparations is diabetes mellitus, and it will be quickly apparent that these products cause a considerable increase in the elimination of sugar. We have already seen how this is brought about.

Lucien and Parisot[39] mention a case of diabetes in which the amount of sugar was largely increased, not merely for a few hours, but for several days, following an injection of $\frac{1}{10}$ milligramme of adrenaline for the performance of a dental operation. This indicates that the action of the adrenaline is not confined to the influence of the actual remedy, but that it is a strong stimulant of the adrenal secretion.* These authorities also warn against the possibilities of untoward reactions in cachectic individuals and those who are very debilitated. Naturally, hypertension is an important contra-indication, and with it, of course, must be included vascular disease, atheroma, aneurism, etc.

The instillation of a weak *adrenalin* solution into the conjunctival sac may cause, in patients with hyperadrenia, serious palpitation, dyspnœa, and general weakness. This is sufficient indication for extreme care in the employment of this potent remedy and in cases of known adrenal overactivity (diabetes, hypertension, etc.) it should be used only in great necessity. One should also institute adrenal therapy with very small doses, in order to test the susceptibilities of each patient to its action, and to obviate unfortunate results which in not a few recorded cases have had a fatal outcome.

* In spite of this it may be read in a pamphlet circulated by a prominent manufacturer that "suprarenal substance has been highly recommended by authorities in . . . diabetes" —surely only in the installation test already mentioned in this chapter. Dr. Sajous comments on this as follows: "Care is necessary here. Adrenal gland is sometimes useful in the asthenic form."

The activity of adrenal preparations may be a detriment, and, unfortunately, untoward results are not uncommon. Donaldson[40] considers this side of the subject, and wisely recommends care in the selection of cases as well as in the administration of the remedy.

Although we have seen that there are certain common indications for adrenal and pituitary (posterior) medication, especially in shock, hæmorrhage, etc., adrenaline cannot be used as an oxytocic, for as a matter of fact such an application would be likely to be attended by unfortunate results, since adrenaline has a relaxing action upon the uterus.

Adrenalin is distinctly contra-indicated in hæmoptysis, and, according to Sergent,[26] when adrenal preparations have been given to tuberculous patients, they should be immediately stopped if pulmonary hæmorrhage occurs.

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CHAPTER XIX

THE HYPOPHYSIS OR PITUITARY BODY

Histologic Structure and Physiologic Action—Schäfer's Outline of the Functions and Relations of the Pituitary—The Physiological Action of Pituitary Extract—The Manifestations and Treatment of Pituitary Disease—The Active Principles of the Pituitary—Pituitary Therapeutics—The Effect on Shock and Collapse—Pituitary Extract in Labour—The Contra-Indications in Obstetrics—In Gynæcological Practice—The Influence on Amenorrhœa—An Enterokinetic or Peristaltic Excitant—The Value in Post-Operative Intestinal Disturbances—The Action on Diuresis—Diabetes Insipidus and the Pituitary—The Control of Polyuria with Pituitrin—The Galactagogue Action—Pituitary Extract in threatened Mammary Abscess—The Tonic Effect of Pituitary Powder—A Hypotensive Pituitary Extract—Miscellaneous Therapeutic Possibilities—The Differences between Pituitary Preparations—Methods of Administration—Dosage—Contra-Indications.

THE internal secretory organs have given investigators many a surprise, and not least remarkable is the information that has been obtained by studying the hypophysis or pituitary body.

While the existence of this organ has been known for ages—it is asserted by some writers that in the days of priest-medicine this gland was considered to be the envelope of the soul—the present-day knowledge of the physiology of the pituitary, and more especially its therapeutic possibilities, is of quite recent discovery.

Not so long ago the pituitary was called by the French *l'organe énigmatique*, but now that the riddle is being solved, it is almost as hard to believe the truth concerning

the importance of this organ and the action of its extracts as it is to realize how ignorant we have been.

Histologic Structure and Physiologic Action.—Embryology has taught us that the pituitary body develops from two dissimilar cell aggregates, the one part from the roof of the mouth (Rathke's pouch), and the other from the neural canal or ventricle. The epithelial part is now known as the "anterior lobe," while the smaller neural portion is called the "posterior lobe," or the "infundibulum."

Physiology has explained that the function of the different portions of the pituitary are quite diverse, and histology shows that their structure is also different, the anterior or glandular portion having a yellow or reddish-grey colour, and showing microscopically well-formed columns of cells; while the smaller posterior lobe is of a whitish colour, and under the microscope shows much connective tissue, fibres, neuroglia, and eosinophile cells. Between the lobes, and connecting them, is a third portion, the so-called "pars nervosa" or "pars intermedia," which consists almost wholly of cellular tissue, which has been compared to neuroglia fibres, and containing many basophile cells.

Some still insist that the pituitary is virtually an aberrant thyroid (Gauthier[1]), but this is most unlikely, although it is not impossible that there may be some developmental relation between the anterior lobe, which will shortly be mentioned.

The whole study of the subject has been rendered difficult by the inaccessibility of this gland, and the danger hitherto associated with experimental operations upon it; but with increasingly efficient surgical procedures and better clinical information our present useful knowledge has been gained.

The clinical study of patients suffering from pituitary

disease has been quite thoroughly outlined, first by the French, and later by American, English, and other writers. Pierre Marie, and later Rénon and Delille of Paris deserve much credit for pioneer work done on this interesting study, and Delille's book[2] must have been a series of surprises when it was first published. Cushing of Harvard has made himself famous by his thorough study of this subject, and his magnificently illustrated monograph[3] gives a concise outline from which one can easily compare the history, clinical and physical findings, and outcome of numerous cases of pituitary disorder.

Schäfer's Outline of the Functions and Relations of the Pituitary.—One of the most concise summaries of our present knowledge of the pituitary hormones is that given by Schäfer,[4] and as it could not well be stated more succinctly, it is given here:

"Some functions of the organ might be conceived to be carried out through the agency of the nerves, but it is much more probable that the gland produces its action by means of chemical agents or hormones, which pass either directly or indirectly into the blood, and through this fluid influence other and distant organs. No hormone has hitherto been separated from the pars anterior, but there is reason to believe that its influence on growth is not produced through nerves. . . . It is difficult to explain the fact of hyperplasia of the pars anterior in producing the hypertrophy which occurs in acromegalics otherwise than by assuming that the enlarged gland is giving a greater amount than normal of a hormone which stimulates the growth of the skeleton, and probably of connective tissue generally.

"The hormone obtained from the posterior lobe resembles in some of its effects the hormone obtained from the medulla of the suprarenals, but it is both chemi-

cally and physiologically a different body. It is at present uncertain whether there is only one hormone in the saline extract of the posterior lobe.* It is probable, however, that the effects upon secretion are brought about by a different agent or agents from that which causes contraction of involuntary muscle.

"Some relationship appears to exist between the thyroid and the pituitary. This is indicated by pituitary enlargement and the formation within it of colloid-containing vesicles following removal or atrophy of the thyroid. Other tissues may also be influenced, as is evidenced by the symptoms produced on removal or destruction of either gland, amongst these being defects of the nervous system. There also seems to be a correlation between the pituitary and sexual organs, since where supposed pituitary deficiency exists, sexual infantilism is established, secondary sexual characters may remain undeveloped, or in males may exhibit a feminine type." A further consideration of this subject is found in Dunan's[5] paper. The various physiologic effects of these hormones are available in therapeutics, since the active principles are found in suitably prepared extracts of the posterior lobe of the hypophysis.

The Manifestations and Treatment of Pituitary Disease.—Pituitary disease is divided into two distinct groups—those cases in which there is an increased function of the pituitary (hyperpituitarism), and those showing diminished or lost function (hypopituitarism). Clinical findings in these various cases enable us to gather a very good idea of the importance of the pituitary hormones, and to draw many conclusions concerning pituitary therapeutics.

The intricacies of the study of pituitary disease are too complex to be considered here. Cushing has fully

* See Fühner's later conclusions on p. 293.

discussed the various aspects of this subject in his book. It remains for us to refer to the use of pituitary extracts in the treatment of these conditions. Pituitary medication does not cure hypopituitarism, probably for the same reason that Addison's disease is not usually amenable to adrenal therapy, and thyroid therapy will not entirely replace an absent or atrophied gland. There can be no doubt, however, about the value of substitution therapy with pituitary extract. Many cases are on record which show that the continuous use of whole-gland preparations reduces the adiposity so commonly found in these cases, stimulates the skin action as well as the growth of hair, reduces the asthenia, and stimulates the sexual organs, especially in individuals with infantilism and Fröhlich's syndrome (*dystrophia adiposo-genitalis*). Occasionally a seemingly permanent result is mentioned, and there is no relapse after discontinuing the medication. On the other hand, too often there is a recurrence of the symptoms if the necessary dosage is not kept up. The dosage is somewhat indefinite, and must be adjusted to the exigencies of each case. Cushing[6] suggests a good method of estimating the proper dosage in these cases: "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 body 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."

In acromegaly the usual condition of hyperpituitarism may eventually become what is termed "dyspituitarism," and in such cases moderately good results have followed

pituitary medication, while pluriglandular therapy has also been recommended.

It happens that the occasions for applying substitution pituitary therapy are rare, since definite pituitary disease is not common; but the study of the physiological action of the various extracts of the hypophysis will open up a vast field of empirical pituitary therapy which will be seen to be much more frequently available.

The Physiological Action of Pituitary Extract.—It was in 1895 that Schäfer and Oliver[7] studied the influence of numerous glandular extracts, and made the first important announcement regarding the physiological action of extracts of the pituitary gland. They found that watery or saline extracts, even when boiled, raised the blood-pressure and constricted the peripheral bloodvessels. Three years later Howell[8] observed that the property of increasing blood-pressure was confined to the extracts of the posterior lobe alone, and that when the blood-pressure was raised, the pulse was slow. In 1901 Magnus and Schäfer[9] found that this extract was markedly diuretic, and in 1906 Herring and Schäfer[10] observed that, although infundibular extract constricts the arteries in general, it dilates those of the kidneys. King and Stoland[11] have also reported on this phase of the action of pituitary extracts. Wiggers[12] showed that the extract slows the heart and increases the amplitude of its contractions. This writer also noticed that it inhibits the flow of pancreatic juice, and is slightly mydriatic. In addition to this, it was later discovered that pituitary extract causes contraction of involuntary muscles generally, raising blood-pressure, and has a particularly noticeable effect on uterine,* vesical, and intestinal

* A substance with a somewhat similar action upon involuntary muscle is obtained from extracts of intestine, and, unlike pituitary preparations, it reduces blood-pressure. This subject is referred to more fully in Chapter VI.

muscles. Ott and Scott[13] have shown that it promotes the flow of milk, and this observation has since been confirmed by Schäfer and MacKenzie.[14]

The Active Principles of the Pituitary.—The pituitary is one of the few glands from which a definite chemical has been obtained. It is available as the salt of sulphuric acid—*hypophysin sulphate*—and standardized 1 in 1,000 solutions are now put up. Hertzberg[15] tried it in a series of thirty-two parturient women, and found that it combined all the advantages of the usual extracts with few, if any, of the undesirable effects. About one month later Fühner's[16] report appeared, and he evidently refers to the same active principle. Fühner was able to isolate no less than eight different substances from the extract of the infundibular portion of the hypophysis. Only four of these manifested the well-known action upon the uterine musculature. The preparation called *hypophysin* consists of a sterile mixture of these four substances, and thus it has become possible to give, with precise dose and with a definite object in view, the active principles of the pituitary body. Furthermore, this writer's experiments on cats, rabbits, rats, and guinea-pigs have demonstrated that this preparation has a specific action upon the uterus, and that the action upon respiration and blood-pressure occurs only with relatively higher doses than are required to produce the uterine effect.

Pituitary Therapeutics.—From the information collated above, it will be evident that pituitary extracts have an exceptional range of therapeutic possibilities, and in the eighteen years that have passed since Schäfer and Oliver's original discovery, and especially during the last four years, many hundreds of cases are reported which suggest startling possibilities. Without attempting the almost

impossible task of going thoroughly into this literature, a summary can be given which embodies the principal facts brought out by various investigators.

One is tempted to discount statements which attribute to pituitary extract such widely differing possibilities, and were it not for the fact that the deductions are based upon thousands of cases and experiments almost without number, one might be permitted to think that the statements are too good to be true.

Fortunately, there are a number of very good pituitary preparations on the market, and some of the more progressive manufacturers are now standardizing their preparations by physiological tests. Hence personal conviction of their therapeutic value is very quickly and easily obtained in clinical practice. Biedl and several others have a predilection for an extract of the whole gland, and he recommends it in cases where it is desirable to increase blood-pressure, reduce the pulse, stimulate diuresis, improve the appetite and capacity for sleep, and, generally speaking, to combat asthenia and stimulate nutrition. Hallion also, like many French writers, is in favour of preparations made from the whole gland. However, by far the greatest experience has been gained with the use of extract of the posterior lobe, or infundibulum, and at least 200 papers on the value of *pituitrin*, *hypophysin*, infundibulin, and other similar preparations, are to be found in the literature of the last four years.

The Effect on Shock and Collapse.—The principal worth of preparations of the posterior lobe lies in their remarkable contractile influence upon unstriped muscle. This is especially evident in the control of the vascular musculature that is exercised by them in shock. Pituitary

extract* is the remedy *par excellence* in shock, since this condition is essentially a state of vasomotor paralysis, and consequent reduced blood-pressure. Its power of contracting involuntary muscle makes pituitary extract invaluable, for the accumulation of the blood in the large veins (splanchnics) is prevented in this condition. Blair Bell of Liverpool[17] was the first to make a thorough laboratory and clinical study of this subject; and while there are references to the experimental use of pituitary preparations before 1909 (it will be remembered that the tonic effect on the bloodvessels was described by Schäfer and Oliver as far back as 1895), Blair Bell deserves great credit for having given us the first information regarding their clinical possibilities. His conclusions regarding the applicability of infundibulin in surgical shock (as well as in intestinal paresis and uterine atony) are generally accepted; in fact, no operating-room is now considered properly equipped unless a pituitary preparation is at hand to meet the emergency. Adrenal preparations have been quite superseded, at least in this particular condition, for pituitary extract causes a rise in blood-pressure fully as rapid as that produced by *adrenalin*, and has the additional advantages of much greater safety and more prolonged action; for while the influence of adrenal preparations is very transitory and is asserted by some to be followed by undesirable after-effects, that of pituitary is prolonged for hours, and in proper doses is without the least danger. Bernouilli[18] expresses the opinion that "it is possible that pituitary preparations, the stimulant

* In this chapter, as is usual elsewhere in the voluminous literature on pituitary extracts, the extracts referred to are all made from the posterior lobe. As a matter of fact, preparations from the anterior lobe alone are not generally obtainable and are rarely used, for their influence is quite unlike that of infundibular preparations.

action of which is less dangerous and more lasting, will [in shock and collapse] replace in future adrenalin, to which will always remain the chief place as a local anæsthetic and hæmostatic."

Hill[19] of Pittsburgh reports that, thanks to *pituitrin*, shock has become unknown in his service, for he uses it as a prophylactic, giving all laparotomy patients an injection prior to their entering the operating-room, and again every hour for three hours on the return to bed.

Another interesting point which has been mentioned is that infundibulin acts, as is the case with certain drugs, in raising blood-pressure better when the animal or subject is in a condition of shock than under the normal conditions. Dale[20] remarks in this connection that "there is an increasing body of evidence which indicates that the pituitary principle acts on plain muscle more by increasing its sensitiveness to normal stimuli than by acting as a direct stimulant (*cf.* v. Frankl-Hochwart and Fröhlich). In the normal person it causes no rise of blood-pressure; in the experimental animal with high blood-pressure it may even cause a fall. Yet when the pressure is artificially lowered, as by cutting off the vasomotor centre, the tonic effect of pituitary extract on the arteries is great and prolonged."

Pituitary Extract in Labour.—Most remarkable of all is the physiologic stimulation of the uterus that is made possible by injecting pituitary extract. The credit for this important discovery belongs to Dale[21] of the Wellcome Research Laboratories, although he did not then recognize its potential value or suggest its clinical use.

It is probably the ideal oxytocic and uterine hæmostat. Blair Bell,[17] working independently, foresaw the obstetric

possibilities of pituitary extract, and recorded cases illustrating its value in this respect as a result of his experimental work carried out in conjunction with Hick.[21a] In 1909 he wrote: "I am inclined to think that in the future we shall rely on infundibular extract to produce contractions of the uterus in many serious obstetric complications, although in my opinion it ought but rarely to be given before delivery." However, it was about a year later that Hofbauer's[22] paper started a veritable avalanche of reports on the obstetric value of pituitary extract. The prompt results obtained in difficult and delayed labour place this substance far above the old methods of uterine stimulation. Intramuscular injections are often active in five minutes or less, and the effects following its proper administration are apparently not harmful to either mother or child.* Blair Bell intimates that pituitary extract exercises a selective action which is more apparent upon the pregnant uterus, and states that "not only are the contractions in the human uterus made more powerful, but they are more prolonged than are those produced by any other preparation. There is little doubt that this preparation acts on the atonic uterus as well as, if not better than, on the contracting organ."

A very good résumé of the value of pituitary extract in obstetrical practice is contained in a paper by Watson,[25] who sums up his experience as follows:

1. Pituitary extracts have a powerful effect in inducing and in strengthening uterine contractions.

2. The type of contractions induced is similar to that

* There are isolated cases on record where the child died after delivery, the pulse being very slow during the short period of its life. These almost invariably can be traced to ignorance in the administration of this remedy (see Spaeth's articles).[23] Then, too, pituitary extract does not always act so rapidly or with average dosage, and very rarely seems to have no favourable influence upon the uterus at all.[24]

which occurs normally, although at first there may be a tendency to prolongation of the pains.

3. Such prolonged contractions result in slowing of the fœtal heart, but the child is seldom in danger.

4. When given in the late part of the first and in the second stage of full-time labour, the polarity of the uterine contractions is not interfered with; but in early abortions and early in the first stage, a simultaneous spasm of the os may occur.

5. Its chief field of usefulness is in the first and second stages of labour when there is delay due to feebleness of the pains, alone or when combined with other complications, such as malpositions of the head, malpresentations, multiple pregnancy, slight narrowing of the pelvis, etc.

6. In the induction of abortion, in the treatment of abortion already in progress, and in incomplete abortion, its action is so uncertain that it is not to be recommended except in cases where the os is widely dilated.

7. In the induction of premature labour its effects are uncertain, but if sufficient dosage is given, they may be good.

8. In the induction of labour at full term and after, better results are obtained than in premature cases.

9. It gives good results in many cases of post-partum hæmorrhage, but is not superior to the various preparations of ergot. It has the power of sensitizing the uterus, so as to allow these preparations to act more powerfully, the combination being most effective.

10. It is a useful adjunct in the treatment of placenta prævia, used in conjunction with rupture of the membranes, the use of hydrostatic dilators, or turning.

It is obviously impossible to refer even briefly to all the papers on this subject. It is fair to state that the

majority of writers on the use of pituitary preparations in labour are decidedly in favour of it, and many write in an enthusiastic vein. One paper, by Vogt[26] of Dresden, describes experiences with *pituitrin* in over 100 cases. The results were both uniform and encouraging. It was used in all stages of labour, the majority receiving it during the second stage. Vogt writes: "It failed only once. In all other instances its action was very pronounced; and although we encounter a great many cases of narrow pelvis in Dresden (from 40 to 50 per cent.), it was not necessary to have recourse to forceps delivery in a single instance in which *pituitrin* was employed. . . . According to our experience, it is the most ideal oxytocic we possess to-day."

It is extremely important to know just how, and especially when, to administer this remedy. It is best given by intramuscular injection, and the dose is usually 1 c.c., sometimes less, of a solution corresponding to 20 grammes of fresh gland, or a 20 per cent. solution. It should preferably be given in the late stages of labour, after the pains have weakened a little, or when it seems necessary to hasten matters. The best results follow its use when the head is on the perineum, and the pains are weak or come on at long intervals. Given during expulsion, this remedy often obviates the need of forceps. Second doses are occasionally necessary, but do not cause a full effect unless an hour, or preferably more, has elapsed since the first dose was given.

In prolonged labour pituitary extract shortens the period of waiting in a remarkable manner. This is nicely emphasized by some figures given by Bondy[27] of the results in eight out of ten cases treated with *pituitrin*. In the first column are figures showing the duration of labour previous to the injection. and in the second

column the period before delivery. The figures are astonishing:

34	hours	...	...	...	45	minutes.
44	,,	...	...	...	30	,,
48	,,	...	...	...	15	,,
23	,,	...	...	...	5	,,
36	,,	...	...	...	35	,,
27	,,	...	...	...	60	,,
44	,,	...	...	...	10	,,
32	,,	...	...	...	29	,,
Average 36	hours	...	...	...	28	minutes.

Contra-Indications in Obstetrics.—Pituitary preparations should not be used if the pelvis is very narrow or the head very high. If given in the early stages of labour, or when there is rigidity of the cervix, dangerous stricture has been caused. It is manifestly contra-indicated in conditions where there is a risk of uterine rupture, and in cases with cardiac, pulmonary, or renal disease, it should be used with extreme caution. Gussew,[28] however, does not consider such conditions are contra-indications to its use, but states: "On the contrary, œdema completely vanished in eight to eighteen hours, the quantity of albumin in the urine was considerably reduced, and in some cases entirely disappeared."

Some writers have found its activity reduced or absent where fever is present, and others point out that the administration of chloroform and other narcotics (morphine, etc.) hinders its action.

It should never be used early in labour or as an abortifacient, as in abortion or premature labour the prolonged contractions which are caused may seriously interfere with later operative interference, if found necessary. If used early in the course of labour, or in large doses, the fœtal pulse-rate may be considerably reduced (to 80, 60, or even 40 beats per minute). Asphyxia and, very rarely, death of the child have been caused.

In Gynæcological Practice it is evident that while pituitary extract may often be of much service, its therapeutic usefulness is not to be compared to that which is available in obstetrics, as briefly outlined in the preceding pages.

It is undoubtedly a valuable hæmostatic, the contractions of the uterus making it of service especially in postpartum hæmorrhage. There are numerous records of the styptic action of pituitary extract in menorrhagia and hæmorrhage following gynæcological operations, abortion, and even cancer of the uterus. Bab,[29] among numerous other writers, speaks most favourably of this method of treating various forms of uterine hæmorrhage. He writes: "Out of thirty cases which we have treated, in ten the hæmorrhage was arrested on the second day, and only in seven was it necessary to continue the treatment for from four to eight days. It must be admitted that *pituitrin* is a valuable gynæcological styptic. Most remarkable are the cases in which hæmorrhage was arrested after lasting from two to seven weeks; in several of these cases a single subcutaneous injection cured the metrorrhagia."

The Influence in Amenorrhœa.—Paradoxical as it may seem, pituitary extract has been successfully used in establishing or increasing the menstrual flow.

It is now recognized that certain of the ductless glands often vicariously carry on one another's functions, and the pituitary body is known to undergo hypoplasia when the catamenia are arrested by pregnancy. Fromme,[30] therefore, tried injections of *pituglandol* in the treatment of amenorrhœa, after eliminating all cases where incipient phthisis was suspected. One c.c. was injected each day until the desired effect was obtained, or until it was clear that the treatment was doing no good. In five out of

twelve test cases the menses came on promptly; in two they appeared, but the merit of this treatment was less evident; and, lastly, in five Fromme admits that the periods did not reappear, nor was there any evidence that the treatment had any effect, although some of the patients felt, or fancied that they felt, something like the molimina. Thirty c.c. given daily for several weeks seemed harmless even when no menstrual flow appeared. This writer believes that pituitary extract is likely to answer in cases where young women become corpulent as the amenorrhœa develops, the fatty change being related in some way to disturbances in the ductless glands.

Leonard Williams[31] relates an interesting case of amenorrhœa which, after "a perfect orgie of treatment—medicinal, surgical, and suggestional—into the details of which it would be painful to enter," was controlled with whole pituitary extract in doses of 10 grains (0·7 gramme) three times a day. In this case the amenorrhœa recurred after discontinuing this medication, and the flow re-appeared after recommencing it.

An Enterokinetic or Peristaltic Excitant.—A similar action of the pituitary extract to that upon the uterus, bladder, and bloodvessels, is obtainable upon the intestinal musculature, and various pituitary extracts have been used with good results in intestinal atony and paresis, especially in post-operative cases. Blair Bell and Hick[21a] first discovered this action, and used it in clinical practice.

Houssay and Beruti[32] of Buenos Aires maintain that fluid pituitary preparations constitute the most efficient agent now available for bringing about intestinal contractions. This enterokinetic influence has been frequently mentioned, but rarely used until these writers

suggested that this particular virtue had not been generally recognized because insufficient doses had been used. The dose for the purpose should be larger than that used as an oxytocic. Two c.c. of a 20 per cent. solution is the proper dose for adults, and will induce defæcation in 88 per cent. of all cases. Within two or three minutes after the subcutaneous injection, the patient becomes conscious of intestinal movements, and almost always within six to sixty minutes evacuation follows. Slight pain is often experienced; pallor is also a customary symptom, and the pulse-rate increases. The bowel movement may recur on the day of the injection, and frequently remains satisfactory on the succeeding day or two. In fæcal impaction the drug may be given in conjunction with mechanical treatment and enemata. In addition to its use as a prophylactic and curative agent in post-operative intestinal paresis, pituitary extract permits of the use of morphine in cases where its employment would otherwise be unjustifiable, counteracting the paralyzing effect of morphine on the intestine, and preventing meteorism. In peritonitis the favourable effect of the extract on the intestinal and general circulations and its diuretic action are also of value. A tonic effect on the bowel can be secured by continued use. Small hypodermic doses are stated to stimulate gastric motility and increase the flow of gastric juice. Administration by mouth, even in large doses, does not afford results comparable with those already mentioned, and does not appear to be indicated at any time. In a previous communication Houssay[33] (and Ibanez) called attention to the presumed superiority of pituitary preparations over *hormonal.*

The Value in Post-Operative Intestinal Disturbances.—Another extremely useful application of pituitary extract

is of special interest to surgeons. It may be used to relieve annoying post-operative symptoms, such as meteorism and distension. The rapid and irregular pulse which not infrequently accompanies these symptoms is also favourably modified.

Bidwell[34] tried the enterokinetic effect of a solution of pituitary extract in twenty-one laparotomy cases. In three the bowels acted without an enema, and in all but two of the others a simple enema sufficed to bring about a satisfactory action without any aperient by the mouth. All passed flatus freely a few hours after the injection, and were free from abdominal pain or distension. The pulse was much lower than usual, and even after some of the severest operations did not exceed 80 per minute. Bidwell recommends that ½ c.c. should be injected intra-muscularly six hours after operation, and be followed by two or more such doses at six-hour intervals.

Blair Bell,[17] in his first clinical paper, already referred to, relates a case which shows the extent of its value in intestinal atony and paresis. His patient suffered from intestinal obstruction; an operation—ileo-sigmoidostomy—was performed, and calomel in ¼-grain doses was given every two hours without effect. A glycerin enema had no better action. A second operation—right lumbar colotomy—was performed, and more calomel and other drugs, including eserine, were given, without result. Acute obstruction had now existed for five days, vomiting was continuous, and the patient was in great pain from flatulence and distension. An injection of pituitary extract was made into the muscles of the forearm. Within a few minutes the severe distension was reduced, much flatus was passed by the colotomy wound, and immediate relief was obtained.

The Action on Diuresis.—To all the foregoing must be added still two other important physiologic actions. Pituitary extracts have been observed to exert a decided diuretic effect, which seems to be due to a selective influence of one of the contained hormones upon the cells of the renal tubules. Small doses of the extract given by mouth or hypodermically produced a prolonged and decided diuresis, and this, combined with the effects upon the heart and cardio-vascular system, seems to indicate that pituitary extract in some cases has a better influence than the diuretic group of drugs. This action has been supposed to be due to a special diuretic hormone from the pars intermedia, and it is not 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.

Frequently an increase in micturition results from the administration of pituitary extracts in obstetrics, and many writers mention this incidentally. In shock, too, the diuretic effect is noticeable, and may be the cause of a part of the good effects so generally obtained.

In nephritis with hypotension, such as frequently follows scarlatina and diphtheria, the action upon the kidneys is good, and the general hypertensive and tonic influence is of additional advantage. In the occasional ischurias of the puerperal period pituitary extract quickly causes a marked diuresis. Hofstätter[35] finds that injections of *pituitrin* permanently relieve the majority of the anurias or dysurias following labour or operations.

Uræmia also has been favourably influenced, and the diuretic principle present in extracts of the pituitary deserves consideration in all cases of arrested kidney action. Intravenous injection may be resorted to, and in such cases a pint or more of warm saline solution, to

which 1 c.c. of pituitary extract is added, is a suitable injection.

In vesical paralysis and atony the influence upon urination is twofold. In addition to the direct diuretic action, the tonic action upon the musculature of the bladder makes pituitary extract of considerable utility. French physicians frequently prescribe the dried extract of pituitary in 10 or 20 milligramme (1½ to 3 grain) doses three to five times a day in cases with insufficient urination and kidney disorder.

Diabetes Insipidus and the Pituitary.—Experimentally, a relation between polyuria and pituitary disease has been shown to exist. Frank[36] states that it can be proved clinically, as well as experimentally, that the pars intermedia produces a diuretic hormone, and that diabetes insipidus is due to hyperfunction of this part of the gland. Simmonds[37] also reports clinical and autopsy findings which lead him to conclude that the uropoietic activity, which is pathognomonic of diabetes insipidus, is caused by a hormone produced in the pars intermedia.

Cushing[38] has made many experiments with the elucidation of this point in view. He summarizes his experimental data by saying that—

1. The infundibular region contains, in addition to the substance capable of glycogenolysis, a hormone capable of eliciting diuresis.

2. Under certain operative conditions that entail posterior lobe manipulations there often occurs a diuretic response, and occasionally an extreme diuresis is apt to follow other operative procedures requiring an equally long anæsthetization.

3. Posterior lobe implants may cause a temporary polyuria, which subsides on the removal of the implanted tissue.

4. Certain operative procedures, such as separation of the infundibular stalk and occasionally a simple posterior lobe excision, may call forth a somewhat prolonged polyuria.

In connection with his clinical observations Cushing suggests not only that the emotional polyurias are in all likelihood the expression of a neurogenic discharge of hypophyseal secretion, but also that the clinical polyurias of longer duration are in many instances merely the symptomatic expression of an internal secretory disturbance, brought about by injury or disease involving the hypophyseal neighbourhood. Hence, whether or not there actually proves to be a form of polyuria of primary renal origin, our present conceptions of diabetes insipidus need to be recast, with special reference to the factor of the secretory activity of the pituitary body, and particularly of its posterior lobe.

It is possible that this interesting relation between polyuria and hyperfunction of the pituitary may lead to the use of hormones that are antagonistic to the pituitary hormone with good results.

The Control of Polyuria with Pituitrin.—Francesco[39] of Venice gives a valuable review of the relation of polyuria to pituitary disorders. His experience adds weight to the previous statements regarding the relation of diabetes insipidus to pituitary disease, and at the same time shows the extreme complexity of hormone action,* as he reports in detail, and with charts, two cases of diabetes insipidus which were controlled by injections of *pituitrin*. The average quantity of urine in both cases varied from 6,000 to 8,000 c.c., and when in control from 1,000 to 2,000 c.c. daily. The curve of one case is especially interesting, as from it it appears that interruption of the

* Elsewhere we have noted that pituitary preparations have a decided diuretic effect, and may be used in ischuria as a means of increasing the urinary output. Here the same treatment reduces it.

pituitary treatment for a few days allowed the urinary quantity to rise very materially, while a later substitution of ovarian for pituitary extract caused an equally great rise. A recent editorial[40] consideration of this subject gives a number of additional references, and includes a statement to the effect that Farini also reports that he was able to reduce the polyuria of diabetes insipidus as long as active pituitary treatment was kept up.

The Galactagogue Action.—Last, and by no means least, of the specific activities of pituitary extract is its galactagogue action. We have seen that Ott and Scott[13] were the first to call attention to this, and their experiments have since been confirmed by numerous other investigators. Several other gland extracts exert a similar action, notably that of corpus luteum, epiphysis, and mammæ. Pituitary extract, however, contains the most effective galactagogue hormone, and, suitably combined, has been suggested as a rational and valuable postpartum remedy, both for its galactagogue action as well as for its tonic and antihæmorrhagic influence upon the involuting uterus.

Schäfer[41] states that the effect upon lactation of the injection of pituitary extract is one of the most striking experiments in physiology. The milk pours from the gland in a continuous stream, the flow gradually diminishing and ceasing after ten to fifteen minutes. However, this does not appear to influence milk production, but merely to be an emptying of the gland. It seems as if the alveoli and ducts were contracted and squeezed out the milk, yet no muscle fibres have been found in the alveolar walls. It is difficult to reconcile the large amount of milk and the length of its flow with this idea.*

* Not all agree as to the therapeutic application of this undoubted galactagogue action. Heaney[42] writes: "In conclusion it may be stated with some assurance that the results of experimentation with *pituitrin* upon lactating

Gavin[43] finds that the administration of extracts of pituitary body and corpus luteum to dairy cows, by the mouth or by subcutaneous or intravenous injection, causes practically no alteration in the total quantity per diem or in the quality of the milk; while, on the other hand, Schäfer records having given pituitary and corpus luteum extracts to a young married woman nursing her second baby, and states that there is ample evidence of the positive effect of these extracts, especially as regards the pituitary extract.

Sutherland Simpson of Cornell, in a personal communication, suggests that Gavin's dosage was too small, and writes of a series of experiments upon goats. In his letter is the following interesting statement: "What we found was this—when milked about fifteen minutes after injection, the yield was about doubled, but there was a corresponding diminution at the next milking, so that there was little if any increase in the total twenty-four-hour quantity. The milk withdrawn after the injection, however, was found to be very rich in fat; on one occasion it contained as much as 18 per cent. of fat, about four and one-half times the normal quantity. The fat at the second milking did not fall below the normal, but was usually still a little above. The other constituents of the milk did not appear to be affected."

Pituitary Extract in threatened Mammary Abscess.—The galactagogue action which has just been considered may be used to good advantage where there is stasis of the fluids in the breast and a threatened abscess formation, since the stimulating or expressing action is useful when

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animals and humans do not support the assumption of its galactagogic effect. The stimulus which it appears in some cases to give to the milk flow should probably be explained by the effect in contracting the smooth muscle fibres of the breast, and this very fact makes it probable that its continued administration would discourage rather than stimulate the secretion of milk "

the ducts are blocked with pus. White[44] considers pituitary extract very useful in aborting threatened abscess of the breast, and found that, in addition to facilitating absorption of the gathering, this medication, which was supplemented with *lactagol* (a proprietary extract of cotton-seed), facilitated an abundant secretion of milk. He reports the case of a woman with a threatened mammary abscess who was enabled to nurse triplets for seven months, as a result of this combined medication.

The Tonic Effect of Pituitary Powder.—The general physiologic effects of pituitary extract can be used in the treatment of numerous conditions. Small and persistent doses of the total extract, especially when combined with suitable amounts of other synergistic hormone-bearing extracts, exercise a tonic effect that is quite advantageous, and seems to be more particularly evident in the neuro-muscular system. As a means of combating asthenia it seems equal to, if not better than, the usual vegetable and mineral tonics; and this is amplified by the fact that it favours the appetite, increases nutrition, and facilitates sleep, as is emphasized especially by Delille.[2] In the neurasthenias which are accompanied by hypotension, and n myocardial asthenias, pituitary extract often gives satisfaction; the pulse is slowed while the pressure is raised.

Musser[45] records his experience with the oral administration of a total dry extract of pituitary in eighteen cases. Its most constant influence was upon the blood-pressure; in seventeen of the cases it rose, the highest rise being 28 millimetres. Several of the cases were subjectively benefited by this pressor effect. The other results were variable and somewhat less definite. Six patients noted a diuretic effect, but there was no particular change in the urinary constituents. A diarrhœa developed in seven

cases; and four, previously costive, had regular movements whilst taking the extract.

Jaschke[46] concludes that pituitary extract is an excellent general tonic after operations. He used it in forty-four cases, and states that it is possible to increase the action of the cardio-vascular mechanism, and in the majority of cases to stimulate the action of the bladder. Combined with saline injections, he found it particularly useful in those cases in which chloroform has been employed as the anæsthetic.

A Hypotensive Pituitary Extract.—It has been known for some time that under certain conditions the hypertensive action of injections of pituitary extract could be changed to a hypotensive reaction, and Schäfer, Howell, and others, have shown that the alcoholic extract of pituitary maceration separated certain depressor substances, while the pressor substances remain in the albuminous residuum.

Claude and Baudouin[47] have outlined a method of isolating this extract, and in a later communication[48] Claude considers the diversity of action of various hypophyseal products which depends upon the method of preparing them. These investigators have shown that by suitable procedures, chief among which is the removal of the lipoids from the glandular maceration (of the posterior lobe), they could secure a substance, with considerable depressor activity, which has more than experimental value, for they relate its application in several cases of hæmoptysis in which the good results are illustrated by graphic curves.

If the possibilities just outlined are more generally conceded, it seems that another extremely valuable agent will be available, for chief among the disadvantages of pituitary medication is the fact that its pressor influence

is too often inconvenient. Many cases which would be the better for certain of the tonic and reconstructive effects of total pituitary extract, have too high a blood-pressure to allow of its effective administration. It is entirely probable that other pituitary preparations, with different properties than those at present on the market, will eventually be available in clinical practice.

Miscellaneous Therapeutic Possibilities.—In addition to the already long list of conditions in which the administration of pituitary extract is useful, there are several disorders in which this preparation has been occasionally prescribed.

Wallace and Child[49] present a preliminary report on the use of pituitary extract in rheumatoid arthritis, giving the histories of ten cases, five of which were hospital cases in children, and five in adults in private practice. All the patients showed improvement in the general condition, in the pains, in the swellings and motions of the joints affected, and in the effect on the bowels. The blood-pressure was elevated throughout the treatment, and had a tendency to remain so. There was a slight irregular rise in temperature during the first week or ten days. In one of the children the prognosis under the treatment was changed from fatal to favourable. The adult patients were slightly nauseated and suffered from head symptoms, such as giddiness, lightness, and headache.

Klotz[50] reports good results from the pituitary treatment of rickets in children, and strongly recommends its use in this disease. In osteomalacia also good results have been recorded, and it has also been recommended in hyperthyroidism, although no remarkable results have come to the author's notice. *Pituitrin* has also been used topically for its astringent effect, and it is claimed that this influence is of equal, or perhaps greater, value than

that of *adrenalin* in hay fever and asthma. For this purpose the 1 in 1,000 solution is diluted with two to five times its volume of warm salt solution.

The Differences between Pituitary Preparations.—There are two forms in which pituitary extracts are obtainable—dry, in powder or tablets, and liquid, usually in ampoules. The powdered preparations in France are generally total extracts of the whole gland, and are given chiefly for the tonic and stimulating effects as well as when prolonged glandular feeding is indicated, as in hypopituitarism. The liquid extracts, however, are invariably made from the posterior lobe, and are used most often for their pressor and musculo-tonic action.

The majority of the clinical reports obtainable relate to the liquid preparations, and these vary somewhat in action. Parisot and Mathieu[51] have made a series of comparative tests of certain proprietary extracts. These include Fühner's preparation (*hypophysin*), *pituitrin*, *pituglandol*, and a personally prepared extract from the fresh gland. From the physiologic standpoint, *hypophysin* possesses the essential properties of the extract of the macerated posterior lobe; it manifests particularly a hypertensive and cardio-tonic action. *Pituitrin* is especially cardio-tonic in action, and in a less degree hypertensive. From the toxicologic standpoint, *hypophysin* seems to be the least toxic and *pituglandol* the most toxic.

In a second communication Parisot and Mathieu[52] have reported the comparisons between the actions of these preparations upon smooth muscle. The extracts which show the greatest hypertensive action are those which have the most marked exciting action upon muscular organs such as the uterus. According to these authorities, Fühner's preparation is the most active.

Methods of Administration.—Pituitary extract is not so rapidly diffusible as adrenaline, and therefore is not so quickly absorbed by the gastric mucosa. As it may be destroyed by the pancreatic juice when given *per os*, it should be taken an hour or more before meals. When the general tonic influence or prolonged diuretic or galactagogue effect is desired, oral administration is usually quite satisfactory, but in obstetrical and emergency practice, where it is desired to combat uterine atonia, shock, or other cardiovascular conditions, the intramuscular method is most generally useful. Attention has been called to the fact that pituitary preparations should not be given hypodermically, as necrosis is possible, due to the local vaso-constricting effects of the injection. Occasionally it seems advisable to administer pituitary extract intravenously, in which case the contents of an ampoule should be well diluted with artificial physiologic serum.

Dosage.—There is considerable variation in the strength of various proprietary preparations, so accurate statements regarding definite dosage cannot easily be made. Usually these preparations are put up in ampoules or tablets of known strength, and the dosage is easily controlled. Effective watery extracts contain approximately from 20 to 30 grammes of fresh gland substance per litre, and the dose ranges from ½ to 1 c.c. (8 to 16 minims), while as much as 2 to 3 c.c. may be given in any one case. Ott[53] reports having given as much as 1 ounce of *pituitrin* at a dose, and later intimates that "infundibulin is not very poisonous; it can be used oftener than three times a day if the conditions necessitate it." As far as the less frequently used dried extracts are concerned, each part of the powdered substance or tablets represents from 4 to 5 parts of fresh gland, and the dose varies from ¼ to 1½

grains (0·015 to 0·1 gramme). Small doses in tablet form, frequently repeated, have a general tonic effect.

Contra-Indications.—Manifestly the main contra-indication is hypertension, because of the general hypertensive action of the pituitary hormone. Mairet advises against its use in epilepsy, and reports inconvenience resulting from its use in epileptics. In those diseases in which hyperpituitarism is a factor, pituitary extracts necessarily would be contra-indicated.

In obstetrics there are certain extremely important points, especially regarding the *time* of the injection, which must not be overlooked. They have already been mentioned on p. 300.

Aarons[54] believes that pituitary extract is liable to cause arterial degeneration if used for long, and emphasizes the fact that it is essentially an emergency remedy. This is not generally conceded, however. Thaon[55] advises against the use of pituitary extracts in cases of kidney disease, for he has produced (with quite large doses, it should be remarked) hæmaturia and glomerulitis. The usual dosage would not seem to be contra-indicated because of this experimental work, and many favourable results have been noticed in cases in which there was an unquestioned destruction of a part of the kidney tissue.

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CHAPTER XX

THE EPIPHYSIS OR PINEAL BODY

The Pineal Body as an Endocrinous Organ—The Physiological Action of the Pineal Gland and Extracts thereof—The Relation of the Pituitary and Pineal Glands—The Influence of the Pineal upon Development—The Experiments of Dana and Berkeley—Clinical Conclusions regarding Pineal Medication—Dosage and Administration.

THE firmly established facts concerning the internal secretory activities of the hypophysis not unnaturally have led to the study of the epiphysis with the idea that it might also have a similar action. For some years these two organs have been studied together (*vide* de Cyon,[1] Poppi,[2] etc.).

The Pineal Body as an Endocrinous Organ.—As yet preparations of the pineal gland have not been applied in general practice. This does not indicate, however, that the pineal gland has no influence as an internal secretory organ, or that extracts of this organ have no therapeutic action. From the data which are gradually accumulating in current medical literature, it is evident that the pineal gland is a definite secretory organ, that it produces a hormone, and that its physiological action is transmitted to suitably prepared extracts of this organ. Leading neurologists and other investigators have been clinically testing pineal extracts for some years, with results which seem to be very promising. Hence a few collated statements regarding the function of this organ

and its present and prospective application are quite in order.

As has been the case with practically all the endocrinous glands, it has been pathology which has served to guide us to the study of physiology. The study of the pathological anatomy of children suffering with certain mental manifestations has occasionally indicated the presence of disorders of this pineal gland.

Not every physiologist is agreed that this organ deserves to be classed with the ductless glands. Patten, in his recent work, considers this organ as a remnant of a primitive eye, and in Starling's "Physiology" he says[3]: "The pineal gland has, so far as we know, no functions in metabolism. It is interesting as a vestigeal remnant of a primitive dorsal eye."

Morphologically this may be correct—it is not capable of proof—but so far as the relation to metabolism is concerned, it is evidently a mistake, for modern literature on the subject indicates that changes in the structure of the pineal body often may be associated with disturbances of the metabolism of fat, and evidence seems to be accumulating that obesity may be connected with pineal hypofunction. It has also been stated that children with congenital changes in this organ (hyperfunction) frequently manifest abnormal tallness, an increase in the hair in different parts of the body, together with an increased mental development and premature sexual maturity.

An interesting case, which seems to show the influence of the pineal body upon the mentality, is that of a child in whom a teratomatous hypertrophy of the pineal was diagnosed. So rapid was the mental development, that at five years he reasoned as would a young man, with a predilection for ethics and philosophy!

De Cyon[4] of St. Petersburg has studied this gland for a number of years, and in 1905 suggested that the action of pineal extracts was probably totally due to the salts which were found therein. At that time he believed that the function of the gland was purely mechanical, regulating the entry of the cerebro-spinal fluid into the third ventricle and its exit therefrom; in other words, it automatically controlled the lumen of the aqueduct of Sylvius. Lately, however, his conclusions have been somewhat modified, and while mechanical regulation may possibly be caused by this body, investigations in America by Ott and Scott,[5] Dana and Berkeley,[6] Eyster and Jordan,[7] Bailey and Jelliffe,[8] and others, give us light on a more useful phase of the subject.

The Physiological Action of the Pineal Gland and Extracts thereof.—An interesting study of the functions of the pineal body is published by Kidd,[9] who reviews in detail all that has been published during recent years concerning this gland. He admits that its functions are little known, although at least it is evident that it is no longer looked upon as a rudimentary or disappearing organ, but in all probability it furnishes an internal secretion analogous to those of the other ductless glands. In birds and young mammals this secretion appears to have an inhibitory action on the development of the sexual organs, removal of the gland having produced sexual precocity. Extracts of the pineal body, when administered, act as a diuretic and galactagogue. Cases of tumour of the gland show symptoms of nutritional change, the most typical of these being precocity of the genital apparatus and marked adiposity. The author concludes that the pineal body has two distinct functions, the first being a restraining influence on sexual development, which ceases at puberty, and the second an unknown influence

on the general metabolism of the body, which continues through life.

The pineal gland does not seem to be absolutely essential to the organism. Exner and Boese[10] report that they succeeded in extirpating or destroying the epiphysis in rabbits, and in the 20 per cent. of animals that survived this rather difficult operation, no effects were noticed after the first twenty-four hours. This gland, however, influences certain functions of the body, principally the mental activity and the development of the sexual characteristics.

Ott and Scott confirm the experiences of Eyster, who states that the extracts of the pineal gland have a marked transitory diuretic action by the causation of a considerable increase in the volume of the kidney. Also small proportions of glucose have been found in the urine following pineal injections. These same physiologists notice that the effect of pineal extract upon the uterine muscle was negative, but in the pregnant uterus it increased the contractile power. They also found that it caused vasodilatation in the male genital. All of which goes to prove that there is evidently a connection between the internal secretion of the pineal gland and the hormone balance, which has already been referred to in Chapter III.

The Relation of the Pituitary and Pineal Glands.—There is a similarity between the effects of disease of the pituitary and the pineal, as well as between certain of the physiological activities resulting from injections of extracts of these glands.

Marburg[11] believes that there is an antagonism between the hormone of the epiphysis and the hypophysis, and his opinion is shared by Biach and Hulles.[12] This antagonism is probably the cause of the phenomena frequently seen following the castration of male animals. The

pineal body atrophies, while the pituitary is hypertrophied.

The Influence of the Pineal upon Development.—Berkeley[13] suggests that the pineal gland appears to have a definite and important function—namely, it promotes the development of the human nervous system. How it acts so as to produce this remarkable result can be only matter for surmise at present, but presumably the gland supplies a minute amount of an intracellular ferment accelerating the growth of the grey matter of the brain.

He continues: "In metabolic experiments upon young animals we were able only to hasten their somatic development, but when giving it to defective children we found that in most cases where there was no grave organic defect of the brain, the mentality showed a steady and gratifying improvement lasting over the whole period of administration. It has occurred to me also that pineal gland will not only hurry the slow mind of the defective child, but that it will also arrest or retard many cases of premature senile decay of the mental faculties, thus making it a physiological stimulant or food for the failing powers of old people who yet have no grave organic disease. I have had encouraging success so far, and I hope to report shortly a long series of cases of this kind showing the successes and limitations of the treatment."

The Experiments of Dana and Berkeley.—This promised paper appeared some months later, and it outlines the experiments of Dana and Berkeley.[6*] These were: (1) The nucleoproteids and entire pineal extracts were obtained and injected into the veins to test the effect upon the blood-pressure; (2) they were also injected into

* This is the most comprehensive paper in the English language, and refers to most of the literature on the pineal gland, its anatomy, comparative anatomy, physiology, and pathology. It is especially valuable since it contains the data secured from the treatment of twenty-one cases with pineal extracts.

young animals—rabbits, guinea-pigs—for a long time to determine the effect upon nutrition; (3) the whole gland was given to young animals; (4) the whole gland was given to defective and retarded children. Since the beginning of the summer of 1911 the investigation has been confined almost to feeding experiments. The authors gave the gland to guinea-pigs and rabbits, and to certain selected children, if possible under eight or nine years of age, and to children who seemed to be cases of simple retardation without notable anatomic defect and without epilepsy. Children in the retarded grades of the public schools were used for this purpose, as well as the private cases at the New Jersey Training School for the Feeble-minded at Vineland. The gland was fed to twenty-one children, watching these and comparing them with twenty-one controls. The work was carried on for nearly eight months.

Clinical Conclusions regarding Pineal Medication.—These authors state their provisional conclusions as follows: During the early period of life it has influence over nutrition, including the development of the genital organs, the deposit of subcutaneous fat, general growth, and mental progress. Extracts of the pineal gland of bullocks given to babies caused an increase in metabolic activity, as evinced by increases in the nitrogen eliminated by the urine.

As to the results upon the mental development of the twenty-one children treated thus, they found that as a group they gained 2·23 points. Of the fourteen who gained, the average mental gain is 3·35 points. The control group gained 1·35 points. The gain in standing height for the subjects averaged 18·52 millimetres, while the gain in weight averaged 2·16 kilogrammes. For the controls, the height gain was 24 millimetres, and the

weight 2·89 kilogrammes. There was therefore a slight loss of weight in the treated cases.

Some of the clinical reports of the gain in mental capacity, however, are quite decided, and there seems to be reason to suppose that we are likely to be able to add a new agent to the limited number which seem to have any effect on mental abnormalities. In a recent editorial[14] consideration of this work there is a call for further work in institutions, since no great difficulty should be encountered, and no ill-effects are likely to offset the possible advantages.

Dosage and Administration.—Watery extracts of dried pineal substance are used in experimental work. For clinical practice there seems to be no definite information regarding dosage, save a statement in Dana and Berkeley's paper which follows: "After various unsatisfactory methods of dosage, a physiological dose was adopted, the attempt being made to estimate the actual work that one gland could do instead of its mere weight. Twelve bullocks' pineals, perfectly fresh, are rubbed up with a suitable amount of milk-sugar till extinguished. The mass thus obtained, after thorough drying, is distributed into one hundred capsules. . . . Each capsule is calculated to correspond to 150 pounds of live bullock."

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CHAPTER XXI

THE THERAPEUTIC PRODUCTS OF BRAIN AND NERVE SUBSTANCE

Preparations of Nerve Substance—The Therapeutic Influence of Nerve Extracts—The Antitoxic Action of Cerebral Extracts—Brain Extract in the Treatment of Certain Insanities.

THE principle which underlies the application of extracts of nervous tissue in therapeutics is the fundamental principle of organotherapy. If ingested products made from healthy tissue possess a characteristic action due to their chemical constituents, as well as a supplementary and stimulating action, which results from the influence of extracts of organs upon other similar organs, there should be some basis for the use of extracts of brain and nerve substance as remedial agents.

This subject has been studied by a number of investigators,[1] and for a time seemed to enjoy considerable popularity; but for some reason or other it seems to have been discarded, though recently a number of clinicians have begun to avail themselves of this method of treatment with what they claim to be a warrant of success.

As a means of functionally stimulating the brain and nervous mechanism, there can be no doubt that suitably prepared preparations of this character have some degree of usefulness, for from a chemical standpoint nerve substance contains elements the therapeutic value of which is generally conceded. Chief among these are lecithin

and cholesterin, besides certain other lipoids which have a stimulating action upon the work and nutrition of the nervous system as a whole.

The Preparations of Nerve Substance.—Various authors have recommended different preparations. Some use glycerinated extracts, and administer them by intramuscular injection; others use extracts dissolved in oil and given in the same manner, and a record will be found of a presumably useful preparation which consists of an emulsion of certain substances derived from nerve substance suspended in oil. In addition to the above there are certain preparations which are given by mouth. These include a simple emulsion of brain and nerve substance preserved with glycerine, and desiccated powders prepared from the various parts or the whole of the constituents of the nervous system. Satisfactory dried extracts are not easily made, because of the difficulty of making suitable preparations from a substance so rich in fats as brain is well known to be. Treatment with various solvents, such as acetone, ether, or chloroform, removes, of course, certain of the lipoids, and deprives the product of a good share of the cholesterin and perhaps of the whole of the lecithin, probably the most important therapeutically active agents in brain substance.*

The Therapeutic Influence of Nerve Extracts.—Preparations of this character have been used in the treatment of defects of nutrition, especially where there is involvement of the nervous system. It has been claimed frequently that extracts of brain, spinal cord, and nerve tissue generally exert a favourable influence upon the

* Serono and Palozzi[2] have analyzed brain and nerve substance (cephaline), and find that for the most part it consists of lipoids. There are four principal substances of this nature: (1) lecithin, 3·9 to 4·4 per cent.; (2) cholesterin, 1·4 to 1·6 per cent.; (3) cerebrin, 1·4 per cent.; and homocerebrin, 0·3 to 0·5 per cent.

functional capacity of the nervous system, and by the tonic stimulation of the nutritional activities of this part of the body may cause favourable changes in its functional capacity. The principal conditions in which this treatment has been applied are the functional nervous disorders, such as neurasthenia, hysteria, and certain mental diseases. Where such functional disturbance is accompanied by definite lesions, the results are less likely to be satisfactory; but there seems no doubt from the records that, in spite of organic changes that may have taken place, the reduction of the functional disability of the remaining histologically sound tissue may be of considerable advantage. Rosenthal[3] believes that—"In cases with lesions, even serious lesions, nervous opotherapy acts favourably upon the functional troubles which accompany even medullary sclerosis, and may be employed as a palliative." This same writer concludes his communication to the Paris Société de Thérapeutique[4] with the following statement: "Limited in its precise province, born of an exact conception, responding to a determined indication, combined with other symptomatic medication, nervous opotherapy by the injection of products rich in zymases will justly become a customary factor in practical medicine." This has, however, yet to be accomplished, for at present the extent of the application of this method of treatment is extremely limited.

The Antitoxic Action of Cerebral Extracts.—The "fixing" action of brain substance upon certain poisons was brought into prominent consideration by Wassermann and Takaki[5] in 1898. It was shown that preparations of this character would neutralize the tetanus toxin, and this treatment has been used experimentally to produce an artificial immunity against tetanus. The advent of the antitoxins has relegated the application of

brain extracts in tetanus to the background, but it may be of value to remember this antitoxic action. An extract of brain substance is prepared by Page[6] in the following manner: The brains are dried *in vacuo*, then extracted with ether, and the ether distilled off. The remaining emulsion is dissolved in oil, 1 gramme to each 10 c.c. This product is of a lipoid nature, but is neither lecithin nor cholesterin. Page considers it to be the sole therapeutically active principle of brain substance.

Ten injections, each consisting of 2 c.c. of the solution, are made, one every other day. After an equal period of rest the treatment may be continued. The principal results are thus summarized by Page:

(1) The blood-pressure is raised slightly, and falls again after several hours. (2) The strength, as measured by the dynamometer, is increased. Asthenia rapidly is reduced, and with it the headache. (3) The appetite is increased, and later the weight. The increase may be as much as 2 kilogrammes weekly. (4) Following these injections, there is an increase of phosphates in the urine, a diminution of the conjugate sulphates, and of indican, if present. (5) Occasionally the increased function is accompanied by a mild and passing insomnia. This treatment is recommended in functional nervous and mental diseases generally.

Further evidence of the detoxicating action of this class of substances has been brought forward by Voegtlin and Towles,[7] who found that an aqueous extract of autolyzed spinal cord substance from which the coagulable proteids were removed contained a substance which exerted a favourable action upon experimental polyneuritis. This extract is said to contain an antineuritic substance, which evidently removed the nervous symptoms, but does not re-establish a normal metabolism.

Brain Extract in the Treatment of Certain Insanities.—The original application of extracts of brain in mental disorders seems to have been by Babès.[1] A few years later Ryan[8] and Robertson[9] reported fairly satisfactory results in chronic mania and in melancholia. No extensive work seems to have been done, however, although quite recently Maule Smith[10] states that an extract of brain (of fœtal calves) has given him good results in various forms of insanity. He used it in both chronic and acute cases, and among those which were improved by this treatment were cases of dementia, delusional insanity, dementia præcox, melancholia, and epileptic insanity. The results were, of course, by no means uniform, but the percentage of improvement was good, and no harm resulted from this medication in any case.

Smith prepares the extract by boiling finely divided brain substance in a mixture of alcohol and ether, and straining through muslin. When cold, the deposit is poured into boiling normal saline solution, to which glycerine has been added; 30 c.c. of the deposit with 1 litre of saline solution makes an opalescent emulsion. The extract should be made with fresh brains, and the younger the animal from which they are taken, the more active the preparation. The emulsion contains cholesterin and a substance which reduces Fehling's solution. It is believed to be more active than the dried preparations and *cerebrin*.

Smith does not attempt to explain the therapeutic action of this remedy, but states that it has a powerful influence in various diseased mental states, and doubtless is active in that it induces the re-establishment of a more normal condition of the brain tissue, which is known to be altered in various diseases.

The importance of this subject is the greater because

our present methods of treating the insanities are none too energetic, and in many institutions lean toward the side of passive care rather than to active attempts to cure.

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CHAPTER XXII

THE TESTES—ORCHITIC EXTRACTS

The Renaissance of Organotherapy—The Physiological Action of the Testicular Hormone—The Influence on Growth and Development — Brown-Séquard's Personal Experiences — The Mode of Action of Orchitic Extracts—Von Poehl's Spermin—The Dynamogenic Action of Testicular Extract—The Antitoxic Action in Asthenias and Dermatoses—The Present Status of Orchitic Therapy.

As far as we know, the use of testicular substance was the first of the numerous attempts to use the organs of animals as remedial agents, and the records will show that its use dates back to many hundred years before Christ.

The Renaissance of Organotherapy.—The remarkable and epoch-making studies of Brown-Séquard, published in July, 1889,[1] have placed the use of orchitic extracts upon a much more rational basis, and the results of this work virtually may be considered to be the renaissance of organotherapy.

While to-day this method of treatment is by no means so far advanced as the use of thyroid or adrenal preparations, and many physicians look still askance upon those who manifest an interest in it, preferring to stand by other means of treatment, there can be no doubt that the internal secretion of the testes is a vital factor in the cell metabolism, and that equally with preparations of the ovaries and corpora lutea it deserves application in therapeutics. As a matter of fact, it has been stated

that *didymin* is capable of producing results such as may be expected from ovarian medication.[2]

Unfortunately, a great deal of the literature on this subject is of questionable accuracy, and some of the books seem to have been published with ulterior motives. Suffice it to say, however, that orchitic therapy is useful, and hence worthy of consideration.

The Physiological Action of the Testicular Hormone.—Like several of the endocrinous glands, the testes have a dual rôle in their physiological action, just as their structure falls into two distinct histological definitions, the one part of the gland being the so-called "seminal gland," with spermatogenesis as its function, and the other an interstitial gland having the internal secretory powers which are now so well known. Most of the scientific* knowledge that is available on this subject has come from experiments on animals and pathologic reports.

The influence of castration upon animals is obvious, and from the deductions of hundreds of experiments, which have been amplified by not a few pathologic findings in man, it is clear that the internal secretion of the testes is the principal factor in the establishment of the secondary sexual characteristics. The nutrition is affected in such a way that, when this hormone is absent, the normal vigour and aggressiveness is lost, physical changes in the appearance are obvious, oxidation is diminished, and there is a tendency to obesity and flabbiness. This lack of virility favours the onset of

* Let it be understood that the author admits frankly that, with a very few exceptions, the use of hormone preparations is empiric, and hence not strictly to be classed as scientific. It is only for this reason that organotherapy as a whole has not yet the repute that it deserves; but it is well to remember that empiric methods may be just as rational as those which are absolutely scientific, for in practical medicine one is not so much concerned as to *how* the results are obtained, as that they *are* obtained, and that they are as good and rapid as possible.

premature senility, with undue weakness, changes in the form of the body, facies, etc.

The Influence on Growth and Development.—Experimentally, at least, the removal of the male gonads results in very striking changes in both growth and development, and there is considerable clinical evidence which seems to show that in cases of infantilism, cryptorchism, and occasionally following the removal of the testes, the administration of the corresponding animal extract favours a restoration of the disordered nutrition. In animals, at least, very decided and remarkable changes have been brought about in this manner, although the evidence of the changes brought about in the animals is still denied in some quarters, Gilford having stated, as recently as the Seventeenth International Congress of Medicine (1913), that "all attempts to influence growth and development by extracts from the sex glands have failed." This does not seem to be quite in harmony with the facts, for it has been, and will continue to be, done. It must be remembered, of course, that the administration of preparations of this character cannot begin to take the place of the organs removed, and, if possible, a graft might be attempted which, if successful, will be much more effective in bringing about the desired change than the administration of extracts hypodermically or by mouth.

Brown-Séquard's Personal Experiences.—Numerous clinical tests have been made to establish the physical action of orchitic substance or extract. It has been shown to have a remarkable revivifying influence, and one cannot do better than relate the gist of Brown-Séquard's original communication:

"I am seventy-two years of age. My health is, on the whole, good. Having ceased to take much exercise for

over thirty years, my natural vigour has gradually diminished, and during the last ten years I have become very weak.

" On May 15 I removed the testicles of a vigorous dog. After having chopped up the whole organ, and also the greater portion of the vas deferens, I rubbed up the mixture with a small quantity of water. On filtration, the mixture yielded 4½ c.c. of liquid. I injected into my leg nearly 1 c.c. of this liquid, and repeated the injection on the two following days, as well as on May 24, 29, and 30.

" Before the first injection I was unable to keep on my feet more than half an hour, and even when I remained seated throughout my work in the laboratory three or four hours of experimenting exhausted me. On the day following the first injection, and still more so during the following days, a radical improvement took place. Considerable work at the laboratory hardly produced any fatigue, and to the astonishment of my two principal assistants I was able to do experimental work for several hours in succession in a standing position. My limbs, which I tested with a dynamometer during the week preceding my experiments, and also during the week after the first injection, showed a very considerable gain in strength.

" There can be no doubt that the power of the spinal cord upon the bladder has considerably increased. A radical change also occurred in the reflex action of defæcation. The need of laxatives was much reduced, and the expulsion of fæces could take place without mechanical assistance. There was, in fact, a distinct return to the normal condition which existed many years ago. Brain-work has also become more easy than it had been for a very long time, and I have regained on this ground all that I had lost."

The Mode of Action of Orchitic Extracts.—The conclusions of Brown-Séquard and d'Arsonval,[3] which were made following reports from 1,200 physicians who had clinically applied this method during the first four years of its use (1889-1893), are essentially those of the present time, with the principal exception that the channel of action is now known to be different, the action being through humoral rather than nervous paths. They reached the following conclusions: (1) Though orchitic fluid does not possess any direct curative influence upon the diverse morbid conditions of the system, it may, when injected under the skin, cure or considerably improve diseases, either organic or not, of the most varied character, or at least cause their effects to disappear. (2) These actions of the orchitic liquid are due to two kinds of influences: by means of one of them the nervous system, gaining in strength, is enabled to improve the dynamic or organic condition of the diseased parts, and by the other, which depends upon the introduction into the blood of new materials, this liquid contributes to the cure of morbid conditions by the formation of new cells or other new anatomical elements.

There is no doubt of the stimulating effect of this treatment upon the nervous system, but this nervous action is evidently indirect—that is to say, the orchitic substance does not directly stimulate the nerves. The value of this treatment depends upon the fundamental basis of hormone therapy, which has already been discussed. Not only does Hallion's axiom hold good, but there is a stimulation of the whole hormone-producing system, especially those parts of it which are concerned in the production of energy—the kinetic system—and hence to administer preparations of this character is in the majority of cases to enhance the hormone content of the blood,

and to strengthen the value and frequency of the chemical messages which play such an important part in the maintenance of the vital processes.

Von Poehl's Spermin.—About twenty-five years ago, von Poehl[4] of St. Petersburg, stimulated doubtless by the reports from Paris, suggested that certain organs produced remedial agents with which the organism regenerated itself and overcame disease. He isolated a substance called "spermin" from a number of organs, chiefly from the testicles, and considers it as one of the normal protective agents of the body, which, when given internally, may be also an active remedy. Its administration is merely an imitation of Nature. Spermin is prepared from the testicles of bulls and stallions, which are macerated with water and extracted. The albuminous substances are removed, and the spermin chemically isolated, usually as a salt of phosphoric acid.

This substance has been recommended in a large number of conditions, chief among which is what von Poehl has called "auto-intoxication from decreased intra-organic detoxication." Its value has been stated to be due to its capacity to oxidize the organic acids which originate in the course of a disturbed metabolism, and thus to facilitate the restoration of the normal alkalinity of the blood. This stimulant action upon metabolism is the explanation of its usefulness in certain functional nervous disorders, particularly neurasthenia, which is, after all, virtually a form of auto-intoxication.

Most of the literature on this subject is in Russian, and hence not available to very many. The translation of von Poehl's book* gives his explanation of the rationale of this method of treatment, as well as quite an extensive bibliography.

* See under "Manufacturers' Literature" in the List of Books in Appendix.

The Dynamogenic Action of Testicular Extract.—Clinically, as well as in laboratory experiments, there has been brought together a number of facts which demonstrate that extracts of the testicles contain a principle which acts chiefly upon the energy-producing factors. It will be remembered that the original application of this method of treatment resulted in increased power, both mental and physical. Several experiments have been carried out by Zoth[5] and others with Mosso's ergograph, which conclusively prove that this principle can, and does, influence in a very evident manner the muscular energy. How this is brought about is not quite clear, but it is usually supposed to be due to an increase in oxidation, and the consequent removal of intermediary products of metabolism, which clog the machine. According to Carnot,[6] it produces an excitation of the entire organism by increasing the oxidizing power of the blood, and causing a more complete combustion of the cellular products.

The Antitoxic Action in Asthenias and Dermatoses.—Bouffé[7] has shown that the principal worth of this method in therapeutics is dependent upon an antitoxic action. He calls attention to the frequent benefit following the exhibition of testicular extract in certain toxic dermatoses, and even psoriasis, and considers that these clinical experiences lend weight to his contention of this antitoxic action. A number of other investigators have used preparations of this nature in dermatology, and Scharff[8] is convinced of its value. Bouffé believes that testicular extract may also influence the phosphorus metabolism, thus accounting for part of its good effects. This he has called the "toni-sedative" influence, because the effects often combined sedation of certain functions with stimulation of others. He has found the administration of

testicular extracts to be particularly useful in asthenic states, and especially in those individuals who also manifest an instability of the nervous system.

The Present Status of Orchitic Therapy.—It is difficult to set down the present opinion of this method of treatment. It is not in general use, nor is it of particularly good repute, but nevertheless there can be no question as to its value. The consensus of opinion has been modified by the somewhat highly painted pictures, many of which seemed to be stimulated by more than scientific motives.

The action of testicular extracts is not so limited as we are accustomed to expect. 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.

One particular advantage of this method of treatment, to say the least, is that it facilitates the production of a new supply of substances vital to the economy. The alkaloidal tonics are not superior to organotherapy—at least, in the treatment of chronic conditions—and the action of the alkaloids may be compared to the stimulus of the whip to a tired horse, while the organotherapeutic measures are more like the comparison of a good meal to a hungry one.

There are a number of proprietary testicular extracts

on the market, some in liquid and others in cachet or tablet form. The best known are *didymin* (English), *testikulin* (German), *séquarine* (Swiss), *spermin* (Russian), *orchipina* (Italian), and *orchitine* (French).

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CHAPTER XXIII

THE ACTION OF PROSTATIC EXTRACTS

The Control of Prostatic Hypertrophy—Prostatic Neurasthenia—The Effects upon Bladder Contractility—Administration and Dosage.

THE prostate, like many other glands, has been presumed to have an internal as well as an external secretion. It seems that the evidence to-day is in favour of this theory, although there are many conflicting reports in the literature on this subject. It has been suggested that the prostate influences spermatogenesis, and in consequence extracts of it have been used in the treatment of impotence, but with indifferent results.

The Control of Prostatic Hypertrophy.—There are several published clinical reports of cases of hypertrophy of the prostate in which good results have followed the administration of extract of prostate. Reinert[1] found that both the subjective and objective symptoms were improved, and his experiences have been confirmed by Bazy,[2] Oraison,[3] Englisch,[4] and others. Oppenheimer[5] suggests that this method may be applied in non-specific prostatorrhœa; he found that the discharge was rapidly controlled following several days' treatment with extract of prostate.

These results, however, do not seem to have been sufficiently stimulating to the profession, for of late years there have been very few favourable reports, and outside of France very few attempts are made to apply prostatic organotherapy in genito-urinary practice.

Prostatic Neurasthenia.—The frequency of neurasthenic manifestations in individuals suffering with prostatic disorders has led several investigators to suppose that the prostate supplies some essential element which is concerned in the establishment of the normal control of the nervous system. This seems to be emphasized by Rovsing's statement[6], that individuals frequently become sufferers from melancholia following prostatectomy. Beard[7] also believes that removal of the prostate is a frequent cause of neurasthenia, and that prostatic extract will replace a part of the missing hormone (?), and cause, or at least favour the causation of, a satisfactory control of the neurasthenic manifestations. Other writers agree with this idea, and it seems that the principal indication for prostatic organotherapy is in the treatment of the neuroses that occasionally follow prostatectomy and prostatic hypertrophy.

The Effects upon Bladder Contractility.—Dubois and Boulet[8] assert that freshly prepared watery extract of adult dog's prostate stimulates the movements of the bladder *in vivo*, and that this action is produced just as well in animals with the spinal cord destroyed as in those in which the nervous system is intact; it is, then, independent of the arterial pressure. This may be a part of the explanation of the results obtained in the treatment of prostatic hypertrophy, and especially those cases in which there was retention of urine.

Battez and Boulet[9] reported before the Société de Biologie (Paris) that they had had a fortunate opportunity to corroborate their experiments with extract of canine prostate gland as causing, on intravenous injection, lively contractions of the bladder. Half an hour after his execution they were able to secure a perfectly healthy gland from a criminal, aged twenty years, and to make an

extract therefrom. They found that this human extract had the same effect on the bladder as the canine preparation, and also possessed a marked hypotensive action on arterial pressure.

Administration and Dosage.—The prostate glands of bulls or boars are used in the preparation of the extracts. The gland substance is dried *in vacuo*, and each part of the finished powder represents six parts of the fresh substance.

Extracts of prostate are quite toxic, and it has been shown that 2½ grains (0·16 gramme) of powdered prostate corresponding to 15 grains (1 gramme) of fresh substance are sufficient to kill a dog weighing 17 or 18 pounds. This toxicity is variable, and depends principally upon the age of the animal from which the gland is obtained.

In France prostatic extracts are occasionally prescribed, and the usual dose is 0·10 gramme (1½ grains) to 0·20 gramme (3 grains), two or three times a day.

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CHAPTER XXIV

THE OVARIES AND CORPORA LUTEA

The Discovery of the Ovarian Secretion—Two Ovarian Hormones—The Luteal Internal Secretion—A Pathological Ovarian Hormone—The Influence of the Ovaries upon Metabolism—The Regulation of Calcium Elimination—The Relation between Ovaries and Thyroid—The Influence of the Ovaries upon the Other Endocrinous Organs—Luteal versus *Ovarian Preparations—Ovarian Therapy at the Climacteric—The "Run-Down Conditions"—Amenorrhœa, Anœmia, and Chlorosis—The Vomiting of Pregnancy—Hysteria and Insanity—Miscellaneous Suggested Applications of Ovarian Medication—Hyperoöphorism—Contra-Indications—Dosage and Administration.*

THE ovaries are concerned in the temporary function of the perpetuation of the species, and in the human species are active from puberty to the menopause. During this period they perform a much more complex function than ovulation, for they produce a substance or series of substances concerned in the establishment and correlation of certain of the essential feminine attributes. Their influence extends to the regulation of the intricacies of metabolism and oxidation, and a critical analysis of all the several and rather widely separated ovarian functions demonstrates their fundamental importance, not merely as a pair of ovum-producing organs, but as a remarkable factor in bending the metabolism and regulating the whole reproductive mechanism, as well as the internal secretory system in the preparation for, establishment of, and consummation of, the reproduction of the species.

The Discovery of the Ovarian Secretion.—It appears that Claude Bérnard was the first to suggest the possibility of the dual rôle of the ovaries, while Brown-Séquard,[1] shortly after his notable announcement regarding orchitic extracts, referred to in the previous chapter, expressed his ideas concerning the similarity between the testicular and ovarian juices, and the possibility that the use of ovarian preparations might produce in women results corresponding with those produced by testicular extracts in himself and numerous other men. He was convinced, however, that ovarian extracts are not so powerful as extracts of the male glands.

While the internal secretion of the ovary has not yet been isolated, its influence is very evident. An intimate study of this subject cannot conveniently be gone into here.* It is well known that the removal of the ovaries causes such objective changes as atrophy of the breasts, uterus, and external genitalia, as well as favouring a tendency to obesity, while the subjective symptoms are of a nervous and nutritional character. It is a matter of general knowledge that ovarian disease is frequently the cause of similar disturbances. Many experiments with ovarian grafts in women, as well as in animals, have served to emphasize the vast importance to the economy of the ovarian internal secretion.

Two Ovarian Hormones.—From all the information at hand, it is clear that more than one hormone is produced by the ovary. An "ovarian hormone" is produced by the interstitial stroma of the gland, and is indirectly con-

* There is a large and, at times, somewhat contradictory literature on the functions of the ovary. The subject can only briefly be mentioned here, in order to give an outline basis for the statements regarding *therapeutics* which follow. In addition to the chapters in the reference books (see list in appendix) the papers by Frank,[2] Blair Bell,[3] and Morley,[4] cover the subject very thoroughly, and the last-mentioned paper is amplified by an extensive bibliography of 465 references.

cerned in the regulation of menstruation and nutrition generally. Further, according to Blair Bell,[3] the activity of the uterus is maintained, and regular contractions are promoted, probably by the secretion of the interstitial cells.

On the other hand, the corpus luteum produces a hormone which seems to be an antagonist to the ovarian hormone, in that it "inhibits ovulation between the œstrus periods and ovulation during pregnancy. Ott and Scott[5] have found the corpus luteum to be a galactagogue." Some are of the opinion that this position is wrong, since ovulation has been known to occur during pregnancy.

The Luteal Internal Secretion.—The first reference in the literature to the activities and importance of the luteal cells was made by Prénant[6] in 1898. Fraenkel,[7] shortly after, made an exhaustive report of his studies of the function of these bodies. He believes that the luteal hormone also specifically controls the uterine nutrition during the reproductive life. He has shown also that the corpus luteum is strictly an internal secretory gland, and that it brings about the alterations necessary for the embedding of the ovum, and is therefore essential in the fœtal development in the early part of pregnancy. Fraenkel also believes that the corpus luteum is responsible for the cyclic engorgement of the uterus which precedes menstruation.

The corpus luteum sensitizes the uterine mucosa, rendering it responsive to mechanical stimuli, with the resulting formation of the maternal placenta (Frank).[2] It also inhibits ovulation. This is evidently brought about by a humoral or hormone action, and is essential in the early stages of pregnancy. It might be inferred from this that in certain cases luteal disorder is responsible

for sterility, and lutein might be used to facilitate the attachment of the ovum. Ellice McDonald[8] reports clinical experiences which seem to confirm this idea. He tells of an interesting case of "a woman over forty-five, with commencing menopause, who has been under treatment for three years, with the result that the menses are still regular, and after she had been under treatment for eight months she conceived and miscarried. Her last child was born eighteen years before this. She still continues the medication in the hope that she has discovered the fountain of youth."

The luteal hormone is also an important factor in the growth of the mamma. Frank[2] concludes that—"Growth of the mammary gland is due to ovarian influence (maturation of follicles, activity of corpus luteum). The same factors which produce the persistence of the corpus luteum probably cause the breast hyperplasia of pregnancy." Heape,[9] and later Ancel and Bouin,[10] have shown that the normal production of this hormone causes mammary hypertrophy irrespective of any other usually concomitant factors. They found that in the rabbit ovulation (and consequent formation of a corpus luteum) results only after copulation. With this there is a development of the mammary glands, even though no impregnation follows, the vas of the buck having been tied. They also found that they could artificially rupture the follicle with the same result. O'Donoghue[11] has confirmed this, and his work is referred to, and the relation of the luteal hormone to mammary growth is further considered, in Chapter XXV.

The latest communication of Bouin and Ancel[12] indicates that the luteal hormone is not the only factor in the development of the breasts, but that it renders the mammary cells more sensible to the influence of another

substance, probably a hormone, and is evidently an essential in this preliminary preparatory work.

A Pathological Ovarian Hormone.—Seitz[13] believes that, under certain conditions, a depraved hormone is produced in the ovaries, and that it is the principal exciting cause of uterine fibromata. It may be akin to the "ovarian hormone" which presides over uterine growth and development during puberty, and particularly during pregnancy. This product of ovarian katabolism is probably one of the so-called "parhormones" (Gley). If this supposed relation is real, by its excitation of myomatous growths it is clear that this hormone is no longer physiologic, but the product of a diseased ovary. This accounts for the favourable action of the X rays upon fibroids—the excess of depraved ovarian hormone-stimuli is removed.*

The Influence of the Ovaries upon Metabolism.—The prominent part that the gonads play in the regulation of growth and development is as important as it is easy to demonstrate. The ovaries undoubtedly are a factor in the regulation of the hormone balance, as well as of the metabolism. The facts already referred to have shown that the nutrition of the reproductive system is evidently controlled by these hormones, and a number of experiments have been carried out to show to what extent the ovary and preparations of it modify oxidation and the general cellular activities.

Charrin and Guillemonat[14] showed that ovarian extracts were capable of improving the retarded nutrition which occasionally supervenes in pregnancy—a fact which may justify the assumption that such reductions in metabolism are possibly dependent upon diminished

* Reference to Chapter XXV. will show that the mammary hormone is directly antagonistic to this pathological hormone, and hence is frequently used in the attempt to control myomatous growths and the concomitant uterine hæmorrhages.

ovarian activity. An interesting series of figures secured by Richter[15] from studies of the metabolism in a castrated bitch showed that the metabolic activities, which had been considerably reduced by the operation, were remarkably augmented by the administration of a preparation of ovary.

This seems justification for the results reported by Sicard[16] and others, to the effect that obesity frequently is due to hypo-oöphorism, and that it often may be treated advantageously in this manner. It has been since found that there is a close relation between the ovary and the pituitary body, deficient ovarian activity resulting in a dyspituitarism. In these cases this combination of internal secretory disorders further favours deficient fat oxidation. This fact is also occasionally of diagnostic as well as of therapeutic assistance in the investigation and treatment of obscure disorders in obese girls and young women.

In the asthenic conditions associated with a reduction in the urinary solids the author has frequently noticed that the ovarian treatment of amenorrhœa, climacteric disturbances, etc., caused, besides the more specific effect desired, a considerable increase in the total solids—a fact which emphasizes the evident increased metabolism which this medication occasionally brings about.

Clinical experiments have shown that ovarian therapy increases oxygen consumption, and, according to Offergeld,[33] the internal secretion of the ovary in some manner presides over the metabolism of the inorganic salts, thus regulating and maintaining the chemical composition of the blood.

The Regulation of Calcium Elimination.—The experimental deductions of Blair Bell regarding the calcium excretion following oöphorectomy are worth considera-

tion. He found that this operation diminished the urinary calcium one-half, and believes that "the ovaries take an active part in promoting the excretion of calcium, especially in connection with menstruation."[3] This writer quotes the experiences of Curàtulo and Tarulli,[17] and of Neumann and Vass,[18] who found a reduction in the excretion of calcium and phosphorus after administering ovarian substance. Clinical proof of this position is found in the favourable results in osteomalacia following oöphorectomy, indicating that a condition of calcium retention is brought about in this manner.

The Relation between Ovaries and Thyroid.—Clinical observation will usually show the observer numerous indications that hypo-oöphorism may manifest similar characteristics to hyperthyroidism, and the most plausible interpretation of these facts is that there must be an intimate relation between the thyroid and ovarian hormones.

One has but to recall the frequent enlargement of the thyroid during pregnancy, when ovarian function is dormant, and the remarkable preponderance of Graves's disease in women, to realize the relationship of these two organs.

Further proof of the close connection between the gonads and the thyroid may be adduced from the frequent lack of sexual desire, and even impotence in the male, and the disturbances of the menses in the female, as well as from several reports of favourable results following ovarian therapy in Graves's disease. One of the earliest communications on this subject is that of Seeligmann,[19] who reports three cases of hyperthyroidism, of which one was quite cured, and the other two were definitely improved. Leopold Levi and de Rothschild[20] have mentioned good results following the use of luteal substance in hyperthyroidism which was associated with hypo-oöphorism.

This does not prove that these two glands are antagonistic to one another; rather must one conclude that they supplement one another. There is considerable clinical evidence to show that the addition of small doses of thyroid extract to ovarian medication frequently produces a more satisfactory result, as will be seen later.

The Influence of the Ovaries upon the Other Endocrinous Organs.—A very important communication was made by Blair Bell in his introduction to a discussion on the internal secretions before the Royal Society of Medicine.[21] This writer pointed out that the activities of the ovaries are correlated, and added: "My experiments," he says, "seem to point to a correlated action in so far as the ovary is principally concerned, and an action in regard to the thyroid and pituitary body, which is partly independent, partly correlated. The importance of these assumptions, if true, is obvious; . . . the way seems clearer to the solution of the problem which has so long troubled us—I mean the question of a substitution product in cases of ovarian insufficiency. It seems certain that we shall find that ovarian extract alone is of little value in the majority of cases—in spite of a few favourable reports—because, after ovarian atrophy or removal, the other endocrinous glands are affected, as we have found experimentally, in a way which is different from that which occurs in a case of the removal of one of the other glands; so that the substitution of ovarian extract alone is not sufficient to combat all the metabolic disturbances, or to prevent the changes in the uterus. If, however, we make use of our knowledge of the correlated changes in other glands, I believe before long we shall find a combined extract that will give us some measure of success."

Harrower,[22] in the same discussion, referred to Blair

Bell's intimation that the use of certain combinations of animal extracts is likely to prove of better therapeutic service than ovarian or luteal extracts alone, and "suggested that the results, or lack of results, not uncommonly following ovarian therapy, such as those just mentioned by Leonard Williams, perhaps might have been obviated had a suitable combination been substituted for the single extract. Several French observers, notably Rénon and Delille, have recorded their belief in the advantages of this procedure. This opens up a most complicated, but nevertheless promising, field for therapeutic application, and suggests that possibly in the future pluriglandular therapy may be much more frequently resorted to, with increasingly encouraging results."

Luteal versus Ovarian Preparations.—For a good many years desiccated ovary has been used, with widely varying results. Doubtless much good that has been attributed to it by various writers has really been due to minor concomitant factors which did not receive the full credit due to them. Nowadays, the consensus of opinion is against the total extract, and many reports regarding its uselessness are to be found.

Extracts of the corpus luteum have generally taken the place of the total ovarian extract, for it has been shown that it is much more therapeutically active, and that the results are better with much smaller doses than were necessary with ovarian extract. Drevet[23] considers that the corpus luteum contains the active therapeutic principle of the ovary, and he has used it with good results. Kelly[24] has found good results follow the use of 20-grain doses of lutein extract three times a day, given continuously in certain cases, and for ten-day periods in others. He believes that the total ovarian extract has little or no value.

Ovarian Therapy at the Climacteric.—When the reproductive life is completed, and the genital organs begin to atrophy, the loss of the hormone stimuli to which the body has accustomed itself in the thirty or more years of reproductive life very frequently causes considerable disturbance. This is gradually readjusted in the course of time, but the nervous and mental derangement is often a serious matter. It has seemed reasonable to replace in a degree the lost hormones, and to attempt by ovarian therapy to lessen the severity of these reactions. Among the earliest attempts to apply ovarian substance in the treatment of the disturbances of the menopause is that of Mond.[25] The results were very good, and since then scores of papers have been published extolling this rational method of treating climacteric disorders. The sympathetic neuroses, such as palpitation, flushing, insomnia, amnesia, etc., are often promptly relieved, in some cases for a moderate period, and in others permanently.

Geissler[26] reports good results following ovarian therapy in cases of angina pectoris occurring at the menopause. In certain skin diseases which occur during this period Saafeld[27] noted the disappearance of such skin disorders as eczema and prurigo when ovarian therapy was instituted at the menopause. In metabolic disorders, such as gout, rheumatism, and psoriasis, Seeligmann[19] reported the advantageous use of ovarian preparations, especially in cases which recurred during the menopause. Huchard has used this method in arterio-sclerosis following the menopause, and recommends it.

Merck[29] believes that "we are justified in stating that this remedy is a specific for all troubles occurring at the climacterium, whether this be produced artificially or occur naturally."

The results of this form of medication are, however, not uniformly successful, especially in cases of surgical menopause. One of the fundamentals of hormone therapy —Hallion's law—emphasizes that the administration of animal extracts markedly stimulates the functions of the organs corresponding to that from which the preparation was made. The actual content of the useful therapeutic agent in desiccated corpora lutea is small, and even large doses cannot begin to replace the continuous supply of the ovarian hormones which has so suddenly been removed by operation. It may be slightly useful, although Ellice McDonald[8] believes that its value is practically limited to cases in which the uterus and ovaries, or uterus alone, are retained. He finds it particularly valuable in the treatment of scanty menstruation and the premature menopause. This value is, of course, due to the stimulative action upon the pelvic organs and the augmentation of their output of chemical messengers. McDonald very correctly states that "the internal secretion of the ovary is but one factor in the process of the menstrual life. . . . Let no one expect to control these physical changes and nervous alterations of the surgical menopause by the supply of an artificial internal secretion unless at the same time a new uterus to menstruate can be supplied."

Fraenkel[7] has used lutein with uniformly good results in the disturbances of the menopause, and recommends 0·3 gramme of the extract of the corpus luteum of the cow three times a day.

The "Run-Down" Conditions.—In the so-called "run-down" conditions and neurasthenia, especially in women with ovarian insufficiency, ovarian preparations may be of encouraging usefulness. In many cases of this character their activity is enhanced by the addition of a very small dose ($\frac{1}{10}$ to $\frac{1}{20}$ grain) of thyroid extract, and in cases

with hypotension a small dose of pituitary extract may well be added. It seems that in addition to the local influence of each respective extract, the whole favours the regeneration of the functional activity of the adrenal system, for in many of these cases asthenia, hypotension, and reduced metabolic activity are commonly present (see Chapter XXX.).

Burnam,[30] from personal observations in his own practice, as well as in that of Howard A. Kelly of Baltimore, reports encouraging results from the application of luteal therapy in this class of cases, and writes: "Certainly our most striking results have been obtained with a class of patients usually described as neurasthenics. Most of them are over thirty-five years of age. . . . These patients are excessively nervous, very easily fatigued by either mental or physical work, usually more so at the menstrual periods than at other times. Many improve slowly on rest-cures. Immediately, however, on trying to resume the duties of a normal life, they go back. The general physical, as well as the local pelvic, examinations are entirely negative. . . . It must be clearly understood that this group of symptoms may arise from other causes than insufficient ovarian function. It is, however, astonishing how quickly and completely many such patients will respond to lutean therapy. It has been my custom to give about nine tablets* a day in the ten days before menstruation, to reduce this to six after the flow begins, and in the period from the end of the flow until the next time to give three tablets a day. Often this therapy, carried out for a month, will give relief for many months. The result is, as it were, a re-establishment of a broken compensation between the internal secretory glands."

* Each tablet corresponds to 20 grains of fresh corpus luteum of the sow.

Amenorrhœa, Anæmia, and Chlorosis.—In irregular menstrual conditions, varying from complete amenorrhœa to profuse dysmenorrhœa, Jayle[31] urges ovarian opotherapy. Where anæmia is secondary to general inactivity of the reproductive system, the good results due to this treatment are reflected upon the blood-findings, which are considerably augmented. Bandler[32] states that in certain forms of dysmenorrhœa, which he ascribes to a mild form of hyperthyroidism, ovarian extract is of great value.

Many cases of amenorrhœa are reported by various authors in which a complete cure was accomplished by a longer or shorter course of ovarian or luteal therapy. In some cases it would seem that the introduction from without of a substance containing the ovarian hormones was just the stimulus that the inactive ovaries needed, and with a few weeks of treatment the menses are satisfactorily established. Not all, however, are enthusiastic about its value.

Bandler found ovarian extract to be the best remedy for amenorrhœa, relative and absolute. He believes that combinations of iron, arsenic, and ovarian extract are particularly useful in such cases, and he considers the indication for iron equally an indication for ovarian therapy. For some years Merck has made a combination of their ovarian preparation (*ovaraden*) with an iron salt of nucleinic acid (*ovaraden-triferrin*), which has been highly recommended in the common complex of ovarian insufficiency and anæmia or chlorosis. An article by Offergeld[33] outlines his favourable experiences with this preparation, and numerous other reports might be cited if space permitted.

Several writers have used ovarian preparations in chlorotic girls in whom there was a palpable reduction in

the ovarian activity, with amenorrhœa and general asthenia and suboxidation. Spillmann and Étienne[34] long ago considered chlorosis to be an intoxication of menstrual or ovarian origin, and their success with ovarian therapy was considered by them to be due to the neutralization of the poisonous substances by the ovarian substance itself. This does not appear to be the correct explanation, for it seems well established that the regulation of a disordered hormone balance and the regeneration of a function as important as that of the ovaries cannot but favourably influence hæmatogenesis and nutrition generally.

The Vomiting of Pregnancy.—Several references in the literature praise luteal extract as a means of controlling the disturbances due to toxæmia in pregnancy, Lebreton[35] having used a preparation of ovary with moderately good results as far back as 1899. Stella urges the use of ovarian extracts in hyperemesis gravidarum, and C. H. Mayo[36] states that "vomiting of pregnancy is perhaps best treated by the administration of corpus luteum," although opinion on this subject is not unanimous.

According to Hallion,[37] ovarian extracts have an elective action upon thyroid activity, and in that part of the chapter on the thyroid (Chapter XIII.) which refers to the treatment of the vomiting of pregnancy, several interesting experiences of Naamé with combined ovarian and thyroid extracts are recorded.

Hysteria and Insanity.—A number of reports are on record which indicate the therapeutic value of the ovarian hormones in certain mental disturbances of women. Magalhães[33] succeeded in curing a patient who had been suffering from hysterical crises, which occurred from two to eight times a day. The recent literature on the relation of ovarian disease and insanity is summarized by Dunbar

Hooper,[39] who reports a somewhat remarkable case in point from his own practice. The patient, when he first saw her, was twenty-one years old. She was anæmic and constipated, and had suffered from melancholia for three years, during which time she had menstruated twice only, very scantily, and with great pain. After more than twelve months of treatment, which included curetting, she was placed in an institution, where she spent a year. She was then found to be suffering from religious mania, with amenorrhœa, was occasionally vicious, and at such times refused food. It was decided to remove an ovary, and to substitute for it a more normal organ taken from a sane person. A hysterectomy upon another patient provided the required material, which, after removal, was placed in Ringer's solution at blood-heat. Four and a half hours later the abdomen of the insane woman was opened. Both ovaries were very small, hard, pale, and cirrhotic. The more abnormal of the two was removed, the broad ligament on that side split, and the new ovary, cut into three slices, was embedded in the nest thus provided. Recovery was uneventful, and twenty-four days after the operation a normal, painless, profuse menstruation took place. The mental condition improved rapidly, and in six months the patient was dismissed to her home. She was then menstruating regularly, had put on 6 pounds in weight, and was exceptionally bright and happy. She declared her intention of doing her utmost to repay her parents for the trouble and expense of her treatment; in a word, her insanity had entirely vanished.

Miscellaneous Suggested Applications of Ovarian Medication.—There seems to be no doubt that this form of medication has been rather overdone. The application of the fundamental idea of ovarian opotherapy has been made in several other conditions associated with ovarian

insufficiency. Dalché has tried it in rheumatic conditions, others in such serious nervous manifestations as epilepsy and melancholia, with results which are said to have been encouraging. Of course, the primary indication in all these cases was to supplement a deficient ovarian function which would naturally have a favourable influence upon concomitant conditions. Reference to the aphrodisiac action which not infrequently results from this form of treatment also deserves mention. At present luteal therapy is wisely confined more particularly to the several forms of hypo-oöphorism and their associated disturbances.

Hyperoöphorism.—Manifestly the treatment of this condition can have little to do with ovarian therapeutics, but it is of sufficient interest to deserve a paragraph here, if only to direct attention to those parts of this book in which the treatment is considered more fully.

Excessive ovarian secretion is likely to be manifested by profuse menstruation. It has been demonstrated that the hormones secreted by the ovaries are carried by the blood to the endometrium, where irritation is set up, and such changes as congestion, cell proliferation, œdema, and at times even tissue necrosis, are caused. Sanes[40] puts forward a hypothesis which is of interest. He writes: "It is possible that the degree of intensity of this hormone decides the intensity of the menstrual process—that is, the more active the hormone, and the more susceptible the endometrium, the more extensive and the more destructive are the uterine changes. If, then, the hormones are insufficient to call forth in the uterine stroma the necessary amount of crystalloid material for induction of the œdema, might not the superficial layer remain insufficiently œdematous to allow the blood to break through it? On the other hand, if

the hormones are excessive or the mucosa too sensitive to them, might they not induce destructive changes in the cells, calling out fibrin formation or coagulation necrosis ? . . . May it not be, therefore, that the normal menstruation, with the slight superficial shedding of epithelium and the exfoliation of endometrial shreds or membranes, is the result of the same normal process, the difference being due to the variable degree of intensiveness of the stimulant action of the hormones ?" This is evidently what happens in amenorrhœa, for, as we have already seen, hypo-oöphorism often may be the principal cause, while in hyperoöphorism the effect of the excess of hormone is even worse than the lack of it.

In addition to the excessive menstrual flow in hyperoöphorism, there is often an increased sexual excitability, and with this may be various other associated symptoms and a disordered metabolism, with an unusually large increase in the elimination of lime-salts. Several cases of osteomalacia have been found in hyperoöphorism, and ovariotomy has been practised with good results.

The antagonism of the adrenals to the ovary and corpus luteum has been put to good account by Bossi[41] of Genoa, who suggested the use of adrenal preparations instead of sexual mutilation. Blair Bell[21] suggests the use of pituitary extracts in this connection, and states that "apparently many cures have been effected by this treatment, and also by the injection of pituitary extract. . . . Substitution of other extracts is a great advance on removal of the ovaries in osteomalacia, and the success thus attained indicates the line of attack that will probably be followed in the future in those diseases of the endocrinous organs in which there is an excessive secretion—that is to say, metabolically antagonistic extracts will take the place of removal of portions of the diseased organs."

Contra-Indications.—Swale Vincent states that ovarian extracts should not be given during pregnancy,[42] but it seems that luteal preparations are frequently used, especially in the treatment of the vomiting of pregnancy (*q.v.*). Obviously, also, they are contra-indicated in conditions associated with ovarian hyperactivity—*i.e.*, where mammary preparations are indicated. Menorrhagia may be aggravated by ovarian therapy, and, according to Bandler,[32] the main contra-indication is profuse bleeding.

Dosage and Administration.—Numerous preparations are available, not all of which, however, are uniformly active. Some writers prefer the hypodermic method of administration, but the majority give the various preparations in cachet or tablet form. The dose of ovarian extract is 5 to 8 grains (0·3 – 0·5 gramme) two to four times a day, depending entirely upon the conditions and reaction of the individual to it.

Merck makes two preparations of ovary. In the one, 1 part representing 2 parts of fresh gland, the dose is 15 to 30 grains (1 to 2 grammes) three times a day, and in the other, *ovaraden* 1 part representing 8 parts of fresh gland, the dose is 3 to 6 grains (0·2 to 0·4 gramme).

Most of the older preparations of dried ovary have been superseded by the luteal extracts. These are often prepared from the corpus luteum of the cow, since this organ represents more than one-half of the ovary. Ellice McDonald, in a personal communication, remarks that he knows of cases that have been benefited by cow's ovary (lutein), and not by that from pigs, but has never seen a case benefited by the pig preparation who did not also respond to that made from cows. The products should be as fresh as possible. The dosage is variable, and depends wholly upon the individual needs of the patient and the response to its action. Usually the initial dose

is 2 to 5 grains (0·1 to 0·25 gramme), increasing to 20 or 30 grains (1·25 to 2 grammes), three times a day. Occasionally lutein tablets may cause slight gastric discomfort, and if the dose is large and the treatment prolonged, it may cause a reduction in the blood-pressure.

It is advisable to continue this form of medication for a considerable time. It should be begun immediately after menstruation, in order to affect the succeeding period—*i.e.*, the influence of the hormone, to be most effective, must be felt during the pre-œstrus stage.

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CHAPTER XXV

THE THERAPEUTIC VALUE OF MAMMARY EXTRACTS

The Hormones which activate the Mammæ—The Rôle of Hormones in Mammary Evolution and Function—The Establishment of Mammary Therapeutics—An Antagonist to Ovarian Overactivity—The Control of Uterine Congestion and Hæmorrhage—The Treatment of Uterine Fibroids—An Oxytocic Action—A Reported Neuro-Sedative Action—A Useful Postpartum Remedy—Dosage and Administration.

SUFFICIENT clinical evidence is available to show that the mammary gland, in addition to its galactogenic function, is an integral part of the endocrinous system. Its activities are influenced to a considerable degree by hormones from other internal secretory organs (notably the pituitary, ovaries, and thyroid), and it also produces a hormone, which is concerned in the control of the female reproductive system.

Luncz[1] states that the mammary gland is of the same physiologic character as certain other glands, in that it has a dual function—the production of an external secretion, and also of an internal secretion; and he has shown that it is possible to secure from it a therapeutically active substance which may be used as a means of bringing about those functions which, under ordinary circumstances, it would have caused in the animal from which it was taken.

The Hormones which activate the Mammæ.—Shortly after the announcement of the discovery of secretin and

its important influence upon digestive physiology, another hormone was demonstrated and classified under this title. It was found by Lane-Claypon and Starling[2] that the fœtus *in utero* is the seat of the production of a certain hormone-like substance, the function of which seems to be the stimulation of the mammary glands, first to enlarge, and later to perform their normal function of lactation. These investigators have demonstrated that this hormone can be secured even from the dried embryo, and have prepared it in a similar manner to that of the preparation of secretin from the duodenum. They report that by its influence they have been able to induce lactation even in virgin rabbits. Foà repeated these experiments, using bovine fœtal extracts upon animals of a different species, with the same results as the English investigators.

Previously to this Ribbert,[3] in 1898, had shown that the development of the mammary gland was not controlled by the nervous system. He transplanted a portion of the mamma from a virgin rabbit into a pregnant one, and the transplanted gland developed and secreted milk. Most physiologists are agreed that glandular development and function occur as a result of a chemical stimulus due to a hormone carried into the blood, although Luciani[4] does not yet appear to be convinced of this. It seems that, from the experiences already mentioned above, that hormones which develop and activate the mammary gland are not specific for the species from which they are taken, but their action, as noted by numerous authors, is quite similar to that of the secretins.

These hormones are not the only factors involved in the growth of the mammary gland. Bouin and Ancel[5] have furnished evidence that the corpus luteum—the tissue produced when a follicle of the ovary is ruptured and an ovum discharged—may also be concerned in the develop-

ment of the mammary gland, and lead to its hypertrophy quite independently of the presence of actual products of conception in the uterus. The rupture of ripe follicles can often be induced by purely mechanical or artificial means. The French investigators have shown that such rupture "is ordinarily followed by the formation of corpora lutea, and also by a growth of the mammary glands. . . . These facts serve to lend new emphasis to the dependence of such physiologic responses as mammary development on other than purely nervous relations. They add to the coming significance of hormone activities in the interdependence of various parts of the organism."[6]

This has been confirmed in quite a different manner by a series of experiments on animals, in which it was found that complete ovariotomy resulted in a practical disappearance of the mammæ, and on the successful graft of a piece of ovary in the same animals the lost glands reappeared, showing conclusively the close relation between the ovaries and breasts, and also that the influence depends upon certain chemical messengers, or hormones, and not upon nerve-supply.

The close relation of the breasts and the uterus, as manifested in so common an occurrence as the enlargement of the breasts at puberty, the frequency of pain in the breast during menstruation, the relation of the mammary nerve-supply with that of the clitoris, etc., all go to show that the mammary glands are intimately related to the whole of the pelvic reproductive organs.

A hormone with a similar action has been found in the placenta, which von Basch[7] proved had no connection with the nerve-supply of the breasts. He showed that its administration in other animals, as well as its influence upon transplanted portions of mammary gland, was unquestioned, the cells hypertrophying and producing milk.

Ott has called attention to the fact that the mammary glands of new-born infants are often noticed to be functionating, and suggests that the activating cause is the same as in the mother—the so-called "mamma hormone."

The Rôle of Hormones in Mammary Evolution and Function.—A knowledge of the physiology of the relation of the mammary activities to the various stages of activity of the reproductive organs is of considerable importance, if it is desired to consider mammary opotherapy from a scientific standpoint rather than from the empiric standpoint of our grandfathers.

The most lucid statement upon this subject is to be found in Schil's thesis.[8] This writer, however, is not so interested in the hormones produced by the mammæ as in those which influence the various phases of its development. This may seem a little beside the subject, but it has, nevertheless, a close and essential bearing upon it.

Schil recognizes six stages in the evolution of the mammæ: (1) The *stage of development*, divided into an organogenetic phase and a phase in which there is secretory activity (the lactation of the new-born already referred to). This secretory phase is dependent upon a hormone passing from mother to fœtus through the placenta. This same hormone activates mammary secretion in the mother. (2) The *prepubertal stage*, which lasts until puberty (or the first rut in animals), during which the glands are functionally inactive. (3) The *stage of puberty*, characterized by a considerable increase in the glandular parenchyma. This growth is dependent upon the exciting influence (by means of a hormone) of the mature Graafian follicles in animals, in which non-spontaneous ovulation is produced artificially,* and in

* O'Donoghue[9] and others have artificially ruptured the ripe follicles in animals, and thereby caused a noticeable increase in mammary growth and

the case of spontaneous ovulation to the follicles and the corpora lutea, which develop from these follicles after dehiscence. (4) The *gravid stage*, which is divided into two phases: (*a*) Growth, especially evident during the early part of gestation, as a result of which the glands attain their complete development; and (*b*) a so-called "*phase glandulaire gravidique*," which follows the completion of growth and is characterized by secretory activity, the product of which is known as the "colostrum." Each of these two phases is a result of hormone action, the first due to a kinetogenic hormone from the corpus luteum to pregnancy, and the second to a criticogenic hormone, which seems to come from a secretory portion of the placenta during the second part of gestation, or from a myometrial gland. (5) A *post-partum stage*, continuing during lactation until the glands are again in repose, and divided into two phases: (*a*) Postpartum glandular activity, in which the milk is produced; and (*b*) the phase of postpartum retrogression, in which galactogenesia ceases, and the parenchyma is slightly diminished. Of these two phases only the first is of interest, since the second is caused by an absence of stimuli. The milk, released during pregnancy by an endogenous stimulus, is maintained by an exogenous stimulus—the act of suction. (6) A *senile stage*, associated with involution, and corresponding to the period of cessation of genital activity.

An interesting and convincing proof of the galactagogue action of this hormone is found in the record of the observations of Basch[10] upon the Blazek pyopagous

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activity. The results of these experiments warrant the following conclusion: "The totality of the above evidence appears to justify the conclusion that the corpus luteum is a ductless gland producing a secretion, which is the inciting cause of the growth of the mammary gland."

twins. One of these became pregnant, and was successfully confined, and after delivery, milk secretion also took place in the non-puerperal sister.

The Establishment of Mammary Therapeutics.—On general principles extracts of the mamma, equally with those of the corpus luteum and ovary, should contain certain activating substances which could be used with advantage in those cases where this stimulation seems to be needed. This is fully confirmed by the results of the administration of preparations of this character.

As far back as 1896 Robert Bell[11] of Glasgow proved the physiologic influence of extracts of cows' udders, and indicated their therapeutic value. This seems to be the initiation of the present-day use of this preparation, although dried cow's udder has been known to have a galactagogue action for many years, several pharmacopœias including reference to preparations of dried teats of sheep and cows for the same purpose. Danhardt believes that the breasts also contain a ferment capable of changing albumin into casein, and a Copenhagen physician records his successful use of dried sheep's udder in the treatment of women who were unable to nurse well. His reports state that both the amount and quality of milk were noticeably augmented.

An Antagonist to Ovarian Overactivity.—It seems from the experiences of Hallion and Battuaud,[12] and others, that the mammary hormone is concerned in the hormone balance, as it is antagonistic to the ovarian hormone. Changes in the proportion of these hormones result in disturbances of function, just as changes in the relation of the adrenal and pancreatic hormones result in glycosuria and other manifestations of disturbed sugar combustion. This suggestion is confirmed by the fact that the exhibition of mammary extracts is recommended in

conditions where it is fair to presume that there is ovarian overactivity and uterine underactivity.

Forgue and Massabuan[13] have reported that there may be an evident hypertrophy of the luteal cells of the ovary at the menopause, and, as a result, the hæmorrhages so common at this time are caused by the increased hormone production by the corpus luteum. This is quite in harmony with the ideas just set down, and is further evidence of the soundness of the position of mammary therapy in such cases.

The Control of Uterine Congestion and Hæmorrhage.—The antagonistic action of the mammary and ovarian hormones is probably the most effective antihormone action which is available in therapeutics. Functional overactivity of the pelvic organs is very nicely controlled in this manner. Pochon[14] states that the administration of the mamma hormone* has a tendency to cause uterine depletion, while it is well known that the administration of ovarian extracts tends to increase the uterine blood content.

According to Battuaud,[12] in menorrhagia of young girls this form of medication has proved very valuable, just as it has in the metrorrhagia of the climacteric. Ovarian congestion due to salpingo-oöphoritis and other causes is reduced, although, of course, the influence is purely decongestive, and not directly antagonistic to the infective process. In hæmorrhage due to uterine sclerosis and fibroids, as well as in those indefinite uterine oozings of the menopause which are not associated with malignant growths, this method offers a valuable and physiologic means of control. Batuaud has found it useless in the hæmorrhage resulting from retention of placental frag-

* Pochon means the hormone from the breasts—the mammary hormone. The "mamma hormone" comes from the products of gestation, and, as we have seen, activates the mammæ.

ments, and from mucous or fibrous polypi. A number of writers have called attention to the possibility of diminishing an excessive menstrual flow, and curtailing its undue length by the use of mammary extract. It is also useful in lengthening the abnormally short interval between the catamenia, bringing back the normal rhythm of menstruation as to frequency, amount, and duration. Luncz[1] especially credits this method of treatment with remarkable efficacy, and emphasizes its absolute harmlessness.

A study of other references to the subject cannot but impress one with the antihæmorrhagic and sedative effects of mammary opotherapy in cases of functional overaction of the pelvic organs; but it should be emphasized that preparations of this character are *not styptics*, as a study of their physiologic action will quickly show.

The Treatment of Uterine Fibroids.—While the physiologic antagonism between the mammæ and pelvic organs has been realized for some decades, although the "how" of its action was not settled till the "hormone theory" was brought forward and substantiated, it was Bell's experience in the treatment of uterine fibromata, in 1896, that gave the impetus to the wide study of this subject that has since occupied so many investigators. Bell's first attempts were with thyroid extracts, but he later substituted mammary extracts with very encouraging success. Since then he reports good results from the use of mammary substance in the treatment of uterine fibroids, and mentions a number of cases in which the tumour disappeared or was decidedly diminished in size. He showed that irregular hæmorrhage, as well as the pain, was much diminished, and in some cases disappeared altogether. Shober[16] reports similar results, and recommends mammary extract in fibroids, menorrhagia, and

metrorrhagia, and states that the addition of a small amount of thyroid extract to the dose of mammary extract assures even better results. Feodoroff[17] also found that uterine myomata associated with metritis were favourably influenced by this form of treatment, and that the usual hæmorrhages were considerably reduced. He also noticed that associated mastodynia was relieved. These experiences were confirmed by Pryor and Krause. More recently Feodoroff[18] has published another statistical report of the results secured from the use of mammary extract in the treatment of uterine fibromyomata. He noted a reduction in the size of the tumour in 53 per cent. of all cases treated in this manner. Hæmorrhage and profuse menses were absolutely controlled in 83 per cent. The pain usually noted in the development of the tumour was abolished in 40 per cent., and in only 14 per cent. was there total failure. This author noticed that there seemed to be a secondary influence upon the intestinal function as the bowels were frequently regulated, and there seemed to be a special advantage where meteorism was present.

Mekerttschiantz[19] records fifty personally treated cases, and is most enthusiastic in his praise of this method, which he considers "the touchstone for all cases of uterine fibroids" before deciding upon operative measures. He also applies the same treatment in all forms of uterine congestion.

Luncz[1] prescribes 5 to 10 grains of the dried extract two or three times a day, and suggests its administration before the principal meals. Gastric disturbances are not unlikely, and when they manifest themselves treatment should be immediately stopped. The treatment of fibroids must be continued without interruption for months, and no harm comes from it. Very frequently

the control of uterine hæmorrhage is so marked that an operation which seemed imperative can be dispensed with. If, however, operation is necessary, the course is more favourable under the influence of mammary opotherapy, and where there are definite contra-indications, the operation is the only safe treatment.

An Oxytocic Action.—The active influence which mammary extracts exert on the uterus and adnexa contra-indicate its administration during pregnancy, and reference has been made to an oxytocic action which followed its use.

Schiffmann and Vystavel[20] report that injections of *mammin* had an undeniable abortifacient effect. Four pregnant animals treated with this mammary extract, all aborted. They state that in growing animals injection of the extract of mammary glands from other and the same animals has an inhibitory effect on the development of the reproductive glands and the genitals.

A Reported Neuro-Sedative Action.—Several Russian writers, especially Sellheim,[21] insist upon the sedative action of *mammin* upon the nervous system. This is, of course, more noticeable in females, and this writer reports success in certain cases of neurasthenia, hysteria, epilepsy, etc., which were associated with gynæcologic affections. This seems more likely to be due to the benefits of the control of the pelvic condition, which reflexly influences the nervous state.

A Useful Post-partum Remedy.—It is possible that all these ideas may be applied to advantage in the adjunct treatment following parturition. The tonic influence upon the galactagogue function is much more reasonable than the use of such drugs as atropine and pilocarpine, which are supposed to influence glandular secretion principally through nerve endings, and which

have little influence upon milk production. The author suggests a formula consisting of mammary substance, extract of placenta, and extract of cotton-seed, which, in addition to the galactagogue influence, has a valuable decongestive influence upon the uterus, hastening involution and the return of this organ to the normal. The addition of cotton-seed extract is a result of the experiences of many farmers in giving cotton-seed cakes to their cows. The seeds contain a valuable galactagogue active principle, and the study of a number of Bulletins published by the United States Department of Agriculture should be convincing proof of the relation of cotton-seed feeding to increased milk production.

It has been suggested that the addition of $\frac{1}{4}$ to $\frac{1}{2}$ grain of pituitary extract would be of advantage, as the influence of the pituitary hormone upon milk production is stated by Schäfer to be one of the most striking experiments in physiology. It should be remembered also that the pituitary hormone influences favourably the general nutrition and muscular tonicity; but in those cases where there is hypertension, it is contra-indicated for obvious reasons.

The administration of such a preparation for a few days prior to, and a week or two following, delivery tends to shorten the lying-in period, and increases the important function of lactation, which in these days seems to have taken quite a secondary place in infant feeding, to the detriment of many mothers as well as children. It is well to remember that mothers who do not nurse their children are very frequently subject to utero-ovarian disturbances.

The majority of the authors whose work has already been cited have mentioned a variability of action which must be referred to. There can be no doubt of the action of mammary preparations in suitable cases, and especially

in uterine hæmorrhages; but this influence is unfortunately not constant. In many cases the results are rapid and most encouraging; again the response is moderately good and evident only after some time, while occasionally the effects are quite negative. The author is convinced that this is an important corollary of hormone therapy, and is due to the fact that hormone excess or insufficiency is by no means easily demonstrated, and the degree of the excess or loss can never be demonstrated. This should not be a deterrent to the use of this method; and, reverting to the subject under discussion—the mammary preparations—they are valuable and have proved their worth hundreds of times, and are altogether the most physiologic agents for the control of utero-ovarian superfunction.

Dosage and Administration.—By means of the vacuum-drier one can prepare an active extract of mammary glands, each grain of which represents from 6·5 to 7 grains of the fresh substance. Luncz[1] recommends 0·5 gramme (8 grains) twice a day just before the principal meals. Battuaud also advises this dosage, and suggests that in the attempt to control hæmorrhage between the periods the dose should be continued daily and doubled at the time of hæmorrhage.

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CHAPTER XXVI

THE PLACENTAL HORMONE

The Action of the Placental Secretion—A Galactagogue Hormone—The Rôle of the Placenta in Eclampsia—The Myometrial Gland—The Decidua as an Endocrinous Organ—The Therapeutic Possibilities of Placental Substance—The Influence on Lactation—Uterine Subinvolution—Alopecia and Placental Medication—Administration and Dosage.

SEVERAL of the temporary structures which come into existence during pregnancy serve a double purpose. Principal among them is the placenta, which, in addition to its relation to the fœtal circulation and nutrition, evidently has an internal secretion. It is none too clear whether the placenta and the "myometrial gland," which is shown by Bouin and Ancel to have a distinct internal secretory function, are separate organs, or, like the corpus luteum and ovary, are different parts of the same structure. Reference to some of the literature on the subject may clear up this point.

The Action of the Placental Secretion.—It is believed that the placenta is more than a vascular organ, for a histological examination demonstrates the presence of structures which are closely analogous to glands. Letulle and Larrier[1] in 1901 described certain secreting areas in the placenta, and brought forward scientific proof that the placenta is an internal secretory organ. Halban[2] suggests that the chorionic epithelium of the placenta and ovary exert a similar action upon the body, and that

during the ovarian quiescence of pregnancy the placenta to a certain extent undertakes its work.

Schickele[3] has found that the placenta contains two active substances, the one having the power to hasten the coagulability of the blood, while the other causes prolonged lowering of the blood-pressure. This is in confirmation of Dixon and Taylor's[4] experiments, which showed that placental extract causes a rapid rise of blood-pressure, which was immediately followed by a prolonged fall. It is interesting to note that these investigators also observed that it exerts in a mild degree an influence upon uterine contractility. Fellner[5] of Vienna has done considerable research work on the action of extracts of placenta upon the other female genital organs, and has shown that such extracts have a stimulating influence on the growth of the mamma, uterus, and other parts of the genital tract, but he did not find that the secretion of milk was influenced by it. It seems, however, that there is incontestable evidence to support this, as will shortly be seen.

A Galactagogue Hormone.—Several authorities consider that the principal action of the placenta hormone is the stimulation of the milk-producing activities of the mammæ. Ott and Scott[6] experimentally used an extract of air-dried human placenta, and found that its administration caused increased secretion of milk in a lactating goat. Lederer and Prizbram[7] caused a similar increase of the milk in goats, while Basch[8] injected extracts of the placenta into adult animals which at one time had lactated and produced milk. He also injected these extracts into infants in whom the milk secretion had ceased, but this medication renewed it. He concludes that the so-called "witch's milk" is due to the passage into the fœtus of a hormone circulating in the blood of

the mother. Schäfer,[9] however, intimates that the placental as well as the fœtal ("mamma") hormones produce an inhibitory action on milk secretion.

The Rôle of the Placenta in Eclampsia.—Biedl[10] believes that "the internal secretion of the placenta plays an important part in the modern theory of eclampsia."

It is not definitely known whether the placental hormone is toxic or whether another endotoxin is produced in the abnormal course of events which is the basis of the toxæmias of pregnancy, and especially of eclampsia. Liepmann,[11] at least, shows that, whereas extracts of normal human placenta in large doses are not toxic when injected into rabbits, extracts made from the placenta from patients who suffered from eclampsia proved to be extremely toxic. Many consider that the thyroid normally antagonizes the placental hormone or toxin, and several have suggested that eclampsia is a result of thyroid insufficiency. Schickele has also found that placental extract had a neutralizing action on the depressor influence of thyroid extract when given simultaneously.

The Myometrial Gland.—Ancel and Bouin[12] discovered in the uterine wall of a pregnant rabbit what they have termed the "myometrial gland." They believe that the corpus luteum produces a hormone (see Chapter XXIV.), which stimulates the growth of the mammary gland, but that this action is not evident in the later stages of pregnancy. The hormone of the myometrial gland—in the rabbit, at least—is supposed to be responsible for the activation of the mammary secretion. Some have expressed the opinion that there may be a close structural relation between this gland and the placenta itself.

The Decidua as an Endocrinous Organ.—The decidua, too, has recently been shown to have an action which

seems to be attributable only to a theoretical hormone that is elaborated within it, but it is not on record that it has been used in therapeutics.

Gentili[13] gives a detailed description of experiments with aqueous extracts of the decidua of cows, dogs, and human beings. These extracts proved very toxic when injected in small doses into the circulation of rabbits. Extracts of rabbit and guinea-pig decidua are not so toxic for their own species, though larger doses cause death. The toxic phenomena are very similar to those caused by the injection of extracts of internal secretory glands, but, contrary to the action of these extracts, the decidua extract is more toxic for different species. Animals dying from the injection of decidual extract show similar manifestations to those animals dying from fatal doses of extracts of other organs having internal secretion. There is thrombosis of the pulmonary veins, showing the presence of some substance that favours coagulation of the blood within the body, and it seems that this substance can be neutralized by blood-serum from the same species of animal from which the decidua was taken. In cows particularly, greater toxicity was noted in the early stages of pregnancy.

Aside from its toxic effects, decidua extract always causes a marked fall in blood-pressure. It lessens the force of the systolic wave, and produces disturbance in the cardiac and respiratory rhythm. It is evident from these results that the conjecture that the decidua has an internal secretion is no longer merely a logical supposition, but has been experimentally demonstrated to be a fact.[14]

The Therapeutic Possibilities of Placental Substance.—It is asserted that in certain parts of China the human placenta is considered to be a valuable remedy for the

anæmias that frequently follow the puerperium. Bouchacourt[15] recalls the fact that many animals are in the habit of eating their placenta immediately after delivery, and mentions that this instinctive act is not confined to animals, but that among certain races in Brazil, the Sudan, and remote districts of Asiatic Russia, this rather disgusting habit has persisted. He believes that this may have a favourable influence upon lactation, and brings a series of clinical experiences to confirm his theory.

The Influence on Lactation.—The galactagogue influence of placental preparations may be of service in practical therapeutics, and for a number of years these extracts have been used for this purpose. Bouchacourt reports a case of a young married woman, aged twenty-two, in whom, by administering 2 grammes daily of dried ewe's placenta, he was able to produce a considerable increase in the size of the breasts, with the establishment of a definite colostral flow. A number of other cases were reported, some purely experimental, and others in which a deficient or absent flow of milk in the nursing woman was satisfactorily established. In one case he was able to re-establish lactation in a woman eight months after delivery.

Not all cases will respond to this treatment, although Carnot[16] refers to the observations of several other writers, all of whom record favourable experiences with placental preparations as a means of influencing the production* of milk.

Miklas[17] of Munich has given the most complete and recent consideration of the present possibilities and actual therapeutic value of the placental hormone. He relates

* The action of placental extracts is quite different from that of the posterior lobe of the pituitary. The former seems to influence the *production* of colostrum or milk, while the latter (see Chapter XIX.) acts more as a means of emptying the breasts.

clinical experiences with a number of cases, and concludes that the therapeutic application of placental extract as a galactagogue is still in the experimental stage (in Germany). He is convinced of its value when given by mouth to nursing women, although its action is relatively slight; but he is not so sure of the results in primary hypogalactia. All his work was done with preparations given by mouth, since subcutaneous injections are altogether too painful to be considered.

The administration of preparations of dried placenta is quite harmless, and the reports indicate that there are considerable possibilities in this form of treatment.

Uterine Subinvolution.—Okintschits, in a series of experiments, noticed that the administration of extract of placenta prevented the atrophy of the uterine walls which so uniformly follows extirpation of both ovaries. This gave an idea to Iscovesco,[18] who shortly afterwards tried placental extract in an attempt to modify subinvolution of the uterus. He records several observations in which the administration of this remedy exerted a favourable influence upon uterine involution, and especially in certain cases of chronic hyperplastic metritis which followed accouchement.

Alopecia and Placental Medication.—A most unusual experience has been recorded by Maurice Petit,[19] which is so extraordinary that it seems worth recording as a thought stimulator, if for no other reason. Petit happened at one time to have two cases of alopecia in women which were spontaneously cured during pregnancy. Here is the gist of his communication: One case, a woman of thirty, had had four children, and during each pregnancy the scalp became normal, only to have the bald areas return a few weeks after each delivery. The second case was that of a young woman of twenty-four, with five

areas of alopecia which would not respond to any treat ment. During her first pregnancy the alopecia of years disappeared, only to return two months after delivery. Petit therefore prescribed a cachet of placental extract twice daily for twelve days, with a period of rest for eight days, followed by twelve more days of treatment and eight of rest for several weeks. After two months the cure was complete.

These results doubtless will not last, and lack confirmation, but in spite of this, must be considered evidence that—occasionally, at least—alopecia is a disorder of the endocrinous system, that the placenta has an internal secretory action, which, as in these cases, can be transmitted to pharmaceutical preparations, and used with obvious therapeutic results.

Administration and Dosage.—Quite often the therapeutic value of placental extracts may be enhanced by the addition of mammary extract, and the author has suggested a combination in the previous chapter which in many cases may be useful as a galactagogue and post-partum uterine tonic (see p. 378).

The placental extracts of commerce are usually made from the fresh placentæ of ewes, although occasionally that of the cow is used. It is deprived of its blood, washed, chopped, and dried *in vacuo*, as in the preparation of other animal extracts. The dry powder is quite innocuous when given internally, and represents approximately 15 per cent. by weight of the fresh substances. The dose varies from 3 to 10 grains (0·2 to 0·7 gramme) two to four times a day. Hypodermic injections of aqueous extracts have been discontinued, owing to the excessive local reaction which so often results. Gaifami[20] has shown that this method is accompanied by fever and considerable pain.

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CHAPTER XXVII

PULMONARY OPOTHERAPY

The Action of Lung Extracts—Brunet's Studies—Value in Chronic Pulmonary Infections—The Limitations of this Method of Treatment—Thrombokinase.

For a number of years certain French writers have insisted that preparations of lung tissue have a therapeutic value in a certain class of cases. From time to time papers and case reports have been published which appear to justify this position, and yet, if one excepts the French literature, there is hardly a reference, favourable or unfavourable, to this method of treatment.

The Action of Lung Extracts.—The introduction of preparations of lung substance into therapeutics is attributed to Brunet,[1] a medical officer in the French Navy, who, in a series of experiments on rabbits, found that subcutaneous injections of lung extract possess a tonic action. The pharmacological trials on experimental tuberculosis led to the suggestion that lung extract may serve as a useful auxiliary remedy in the treatment of phthisis. For this reason Brunet decided to use the preparation in man. In a large series of cases of chronic bronchitis and emphysema, chronic and acute tuberculosis, advanced pulmonary and laryngeal phthisis, etc., it is reported that this method of treatment led to an appreciable improvement in the condition of the patients.

Brunet's Studies.—This investigator has devoted much

study to this subject, and his first communication was his thesis[2] (Bordeaux, 1896), which was favourably received, and for which he received the gold medal presented by the Faculty. His serial article on the present position of pulmonary opotherapy is a valuable piece of literature; in it he has gathered together all the references to this method in the literature. It occupies more than one hundred pages, and contains a full bibliography.[1]

Brunet regards pulmonary opotherapy as justified in all chronic diseases of the lungs and the diaphragm, such as chronic bronchitis and pneumonia, asthma, emphysema, fibrinous and purulent pleurisy, abscess of the lung, chronic tuberculosis. The value of this remedy seems to be greater in the chronic purulent infections of the respiratory tract. This writer prepares an extract of lung tissue according to Brown-Séquard's formula, and injects it subcutaneously in doses of 3 to 5 c.c. (45 to 75 minims). He occasionally gives 10 c.c. (160 minims) of the juice with a little water in the morning on an empty stomach.

Value in Chronic Pulmonary Infections.—Arnozan[3] confirmed the good results of this method in the treatment of the more chronic forms of these diseases of the lungs and bronchi, but did not find it so useful in pulmonary tuberculosis. Cassaët observed only a transient improvement and a favourable action on the general condition in phthisis. Grande[4] gave a phthisical patient a dose of 4 to 5 grammes (60 to 75 grains) of the dried organ daily for five months, with the result that the fever disappeared, the sweats and expectoration ceased, and the weight increased. This author also performed experiments on animals which led to the conclusion that this application of organotherapy is of definite use, and is worthy of extended investigation.

Dried lung substance is prepared by Merck for therapeutic purposes from the lung parenchyma of young healthy sheep. The average dose is 5 grammes (75 grains) daily, usually divided into three equal doses.

The Limitations of this Method.—Carnot[5] does not consider that this method is of especial promise, and with the thorough establishment of vaccine therapy for the control of infections, and particularly of bronchial and non-tuberculous infections, and the present position of tuberculin and other indirect forms of hormone therapy as adjuvant measures, it seems that pulmonary opotherapy is not destined to come into general usage. The passage of years at least has not shown any great enthusiasm in this direction, although the work done is sufficiently interesting to be worthy of a brief reference here.

Thrombokinase.—A preparation for the control of hæmorrhage is secured from lung tissue, and may be mentioned. This is the "thrombokinase" suggested by Batelli,[6] and later by Strong.[7] Of course, this is not a hormone preparation. The method of preparation is as follows:

"Sheep's lungs are taken direct into sterile towels, and the larger bronchi are removed to avoid as many bacteria as possible. The lungs are then ground in a meat grinder, and soaked in twice their volume of sterile water for an hour; 1·5 c.c. glacial acetic acid for every litre of extract is then added, drop by drop, with constant stirring. A white flocculent precipitate results, which is immediately collected by centrifuging. The free acetic acid is removed by washing thoroughly with salt solution. The centrifuge tubes are then filled with alcohol, and the mixture is again centrifuged thoroughly, when the alcohol may be decanted, and the nearly dry precipitate may be spread on crystal-

lizing dishes, and rapidly evaporated at a low temperature *in vacuo*."[7]

The chief indication for the use of thrombokinase is hæmorrhage, local application, especially in nose and throat practice, having given very good service. It has also been useful in sporadic and hereditary hæmophilia, and the limited number of reports show that it is valuable in cases where adrenaline fails to render sufficiently permanent help.

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CHAPTER XXVIII

THE CAROTID GLAND

THE carotid gland, discovered by Luschka in 1862, has been considered respectively a nervous structure, a vascular organ, and now a portion of the adrenal system; therefore it should be included in the general discussion of the chromaffin system found in Chapter XVIII.

Not all investigators are convinced even that the carotid gland is an internal secretory organ, although the fact that it has been classed by Kohn[1] with the adrenal system has led some to believe that it produces an internal secretion similar to that of the adrenal bodies.

Frugoni[2] has made numerous experiments with a view to determining whether this organ has a true internal secretion, and in a comparatively recent communication he sums up his conclusions for and against. He is of opinion that an internal secretion is not only possible, but probable; but so far this is a mere hypothesis, for he admits that the results of his experiments are inconclusive.

It is very evident that the action of this small body is not to be compared with that of, for example, the equally small parathyroids or even the pineal body, and hence no attempt has been made to overcome the difficulties in regard to the manufacture of an organotherapeutic preparation, because no advantage is at present known to

accrue from its exhibition to warrant the laborious and expensive task which the preparation of such an extract would undoubtedly be.

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CHAPTER XXIX

LYMPHATIC GLAND EXTRACTS

The Lymph Nodes and the Bodily Defences—The Relation of the Lymph Glands to other Ductless Glands—The Action of the Lymph-Gland Extracts—The Indications of Lymphatic Therapy—An Organotherapeutic Treatment of Adenoids and Enlarged Tonsils—Possible Value in Hodgkin's Disease—Mesenteric Gland Extracts in Scleroderma—The "Lymphoid Compound"—The Preparation of Lymphatic Gland Extracts.

The Lymph Nodes and the Bodily Defences.—It has been asserted now for some time that the lymph nodes are virtually internal secretory organs, and that a part of their capacity to defend the body against bacterial invasion is due to an internal secretion which they produce. This may or may not be true; at present it does not seem to be very thoroughly demonstrated experimentally. Clinical experience, however, has indicated that a certain limited therapeutic value is found in preparations of lymphatic gland substance.

There is no doubt that these organs are an important part of the system of defences of the body, but this does not indicate that their activity is necessarily of a hormone nature. Because of their known phagocytic and hæmopoietic action, it has been presumed that they might contain active principles which would be useful in stimulating phagocytosis and modifying anæmia, and therefore extracts have been made and used in therapeutics to some extent. Either the results of their administration have

been mediocre, or there are other means wherewith to accomplish the same ends more effectively, for references to lymphatic gland therapy are still few and far between.

The Relation of the Lymph Glands to Other Ductless Glands.—A syndrome called "status thymolymphaticus"* is worthy of mention as showing a likely relation between the thymus and lymphatic glands. Its principal manifestations are a persistent or enlarged thymus, which is accompanied by general lymphoid hyperplasia. The patient is usually obese, occasionally rachitic, and very often dies suddenly, with no obvious sign of the cause of death at autopsy. This symptom-complex—it can hardly be called a disease—seems to suggest an endocrinous relationship, which may in time lead to further more useful knowledge.

The Action of Lymph-Gland Extracts.—Experimentally Bartel and Neumann[2] have shown that tubercle bacilli lose their virulence after remaining in contact with emulsions or extracts of lymph glands. This is in harmony with his demonstration that splenic extracts exert a similar influence (see Chapter IX.). Bartel has attempted to apply this antibacterial action in the treatment of experimental tuberculosis, and reports that some encouraging results have been obtained. It is not likely that these findings may be applied in clinical practice, and it should be added that the best results are obtained with freshly prepared extracts—a fact which militates against a very extensive application of this method of treatment.

The Indications of Lymphatic Therapy.—In addition to their use in the treatment of experimental tuberculosis, preparations of lymphatic gland extract have been recommended in streptococcal angina and in adenitis generally.

* For an interesting and recent communication on this subject see the articles of Bierring[1] and others or any recent standard work on medicine.

It is not deniable that there may be a certain modicum of value in this treatment, but in the present author's opinion general tonic treatment by any of the approved methods—even by the suitable application of hormone therapy—and the special treatment of the glands by X ray, local medication, and particularly by the use of suitable bacterial vaccines, is much more likely to be effectual.

It is stated that the administration of lymphatic gland extract causes a favourable leucocytosis, and Perez[3] reports having secured good results from this treatment of tuberculosis, and suggests that it is available not only as a curative treatment, but also in prophylactic or immunizing treatment.

An Organotherapeutic Treatment of Adenoids and Enlarged Tonsils.—Ashby[4] has assumed that the hypertrophy of the tonsils and growth of adenoids is a defensive act of the body, and that this increase in the lymphoid tissue is an attempt on the part of Nature to supply to the organism some secretion which it requires at the particular age when this hypertrophy is most common. It occurred to him that lymphatic gland extract might supply the needed element, and obviate, to some extent at least, the physiologic need for the hypertrophy. He therefore gave to a series of thirty children 5 grains of lymphatic gland extract three times a day for some time. No bad effects were observed; on the contrary, nearly all improved in a very satisfactory way, the snoring and noises in breathing disappeared, and the tonsils have diminished in size.

This preliminary report is of more than passing interest, and it may be that the treatment of benign lymphatic enlargements, and especially adenoids and hypertrophied tonsils, will be materially modified by the introduction of this form of organotherapy.

Possible Value in Hodgkin's Disease.—The destruction of large tracts of the lymphatic system, as in Hodgkin's disease, gives rise to a syndrome in which emaciation and debility are prominent. Whether these symptoms are due to a particular systemic loss, or to the production of deleterious substances, is not yet definitely known; but it has been thought that perhaps lymphatic extracts might be useful as a part of the treatment of this disease. Practically no results are yet on record, and this remains one of the many points regarding glandular therapeutics which are still to be elucidated.

Markwald[5] reports the favourable action of lymph-gland extract in the treatment of a case of Hodgkin's disease. The patient showed an idiosyncrasy to arsenic, and the lymphatic preparation was tried. He states that the size of the enlarged glands was considerably reduced.

Mesenteric Gland Extracts in Scleroderma.—In 1905 Schwerdt[6] attempted the use of extracts of the mesenteric glands of sheep as a remedy for scleroderma. He presumes that this disease is the result of an intestinal toxin which is absorbed, and which should be normally neutralized by hypothetical internal secretions of these glands. If these mesenteric lymph nodes become diseased and unable thoroughly to neutralize these toxins, then the scleroderma occurs. Upon this hypothesis Schwerdt suggested the use of extracts of these glands, and his favourable results indicate that possibly this might be a new addition to organotherapy. His second communication[7] on the subject has been followed lately by two other communications from Kölle,[8] who reports having used 7½ grains daily, of a preparation made by Merck, called *cæliacin*, the dose being later increased to 10 grains. This treatment, continued over a period of six weeks, seemed to be the cause of a striking improvement in appearance as well

as an increase in general health and weight. In his second paper he lends emphasis to his previous suggestion, and although no definite opinions can yet be formed as to the merits of this method of treatment, the results obtained to date indicate that this is a method deserving of consideration in the treatment of similar cases.

The "Lymphoid Compound."—An empirical, but none the less useful, form of organotherapy is embodied in a preparation of lymphatic glands, nervous substance from brain and spinal cord, and testicular substance, called *Lymphoid Compound.* It is difficult to decide which of the ingredients is the most active, and doubtless the specific virtue of the individual elements in the compound varies with the particular needs of the patient to whom it is administered. The neuro-sedative action of the nervous constituent, the defence-stimulant action of the lymphatic constituent, and the well-known tonic and oxidizing action of the orchitic constituent are all useful, and together they make up a combination which has been used with considerable success in conditions in which the nervous and general tone is deficient. Obviously the value of such a preparation is greatest in functional disturbances, but cases of organic disorder—*e.g.*, tabes, etc.—have come to the author's notice in which a restoration of functions supposed to be organically lost was evident. This is probably due not to regeneration of destroyed nerve columns, but rather to the increased responsiveness induced in the remaining sound tracts.

Strangely enough there is practically no "literature" upon this subject, probably because the combination is used principally in England and America, and not in France or Germany. However, this should not militate against the application of this idea in practice, for the administration of a combination of this character is rarely

attended with a reaction of any kind, and offers hope in cases which are usually considered to be hopeless.

The clinical indications for the administration of *Lymphoid Compound* are rather extensive. Generally speaking, it is used in chronic defects of the nervous mechanism in which toxic and nutritional factors are prominent, and as a result functional capacity is reduced. Undoubtedly this form of treatment is active through its influence upon the endocrinous system as a whole, and the benefits which may accrue are due not solely to the remedy itself, but to the hormones and similar substances which its administration seems to call forth.

The Preparation of Lymphatic Gland Extracts.—Particular care should be exercised in the preparation of remedies of this character. It would seem that considerable difficulty is likely to be met with in the attempt to produce suitable products because of the difficulty in obtaining healthy glands. Since the mesenteric and bronchial lymph nodes are often the seat of tuberculosis, particular care must be taken to examine each node separately, not omitting to scrutinize the inside of the gland stroma. It is advisable that in the processes of manufacture all such preparations should be tested upon guinea-pigs, in order to obviate the inclusion of tuberculous material. The preparation already referred to—*cœliacin*—corresponds to equal parts by weight of the gland substance, the quarter which has been removed having been replaced by sugar of milk. The average dose is 5 grains, given two or three times a day, and it is said to be borne without difficulty, but caution is advised in its administration in cases of Graves's disease, as Schwerdt mentions having seen unpleasant results follow its use in one case of this disease.

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CHAPTER XXX

THE USE OF PLURIGLANDULAR EXTRACTS

Unnoticed Endocrinous Disorders—A Guiding Principle in Therapeutics—"Kinetic Therapy"—The "Run-Down Conditions"—The Application of Pluriglandular Therapy—The Relation of Hypoendocrinism to Neurasthenia—Tropical Neurasthenia, or "Punjab Head"—Pluriglandular Therapy in Other Nervous Disorders—The "Jerry-built" Constitution and Hypoendocrinism—The Ductless Glands in Mental Disorders—Opotherapy in Hyposphyxic Conditions—Prospects in the Pluriglandular Treatment of Cancer—The Administration of Antagonist Hormones.

"ALL the protective substances which are involved in the cure of disease are to be regarded as produced by the internal secretions." This, in a few words, is the basis of a new system of therapeutics which hinges upon the action and interaction of the internal secretions. Although the words of Sir Almroth E. Wright, quoted above, are in a sense hypothetical, for we are not yet able to give conclusive *scientific* proof to this effect, the empirical application of this principle has shown that it is evident that the ideas of the great Claude Bérnard have a much wider range of applicability than even he dreamed. We are in the beginning of an era of glandular therapy, which looks extremely promising.

Unnoticed Endocrinous Disorders.—It has already been suggested that the influence of the ductless glands in cases with no *evident* disturbance of any particular one of these organs is worth extended investigation, especially in those individuals with a generally deteriorated func-

tional capacity. With the thought in mind that general disturbances of the internal secretions are very frequently found in these disorders, it seems reasonable to attempt to benefit such cases by the administration of suitably prepared and combined animal extracts, and, while years must elapse before any decided statements can be made, the clinical evidence at hand indicates that good results often follow such treatment.

It appears that the endeavour to influence metabolism in this way is rational, and that hormone therapy deserves to be more frequently associated with those other therapeutic measures which ordinarily would be adopted. It also seems entirely probable that the physical and drug treatment of such conditions will be much more effective if the capacity of the cells to react to such treatment is increased by the simultaneous use of suitable animal extracts.

A Guiding Principle in Therapeutics.—The profound influence that the internal secretions exert upon metabolism explains, on the one hand, why success often follows a change of environment, and, on the other, why there are so many failures in the treatment of certain symptoms-complex. The restoration of the disturbed cell-activities should be one of the guiding principles in all therapeutics, and special assistance is available from suitable pluriglandular combinations. This accounts for the success which so often attends this form of treatment in "run-down conditions," and partially explains the remarkable changes in all the bodily activities which accompany the sanatorium and spa cures. Snowman[1] makes some very sensible remarks on this subject. He writes: "It must be confessed that the general practitioner is only vaguely concerned with the problems of metabolism in his routine work, and that textbooks of therapeutics

hardly proceed in this direction much beyond a general recommendation in most diseases of 'good food, fresh air, and sunlight.' It is often pointed out that recovery from disease is encouraged by such improved conditions. A tardy convalescence is hastened by residence at the sea-side, obstinate anæmia begins to improve in the surroundings of a country life, and chronic indigestion will often refuse to yield until the patient has a 'thorough change.' The true reason that success attends these measures is that they exercise an effect on the metabolism, and tend to restore it to the normal, and then the opportunity is afforded, either to Nature or to Art, to bring about a complete recovery. This endeavour to influence metabolism should therefore accompany the therapeutic measures which may be adopted in any case, and there can be no doubt that if attention to this physiological need became a routine principle in treatment, drugs would achieve more than they do at present."

The frequency with which disturbance in one of the endocrinous organs is followed by, or associated with, changes in both structure and function of others—the evidence of upset of the "hormone balance"—has led several investigators to experiment with various combinations of glandular extracts. Carnot,[2] in this connection, remarks that more recently pluriglandular insufficiencies have become better known, and, in order to profit by certain glandular synergisms, mixed extracts have been used with encouraging results. Commenting editorially on this same subject, the *Lancet*[3] makes the following statement: "If this correlation of effects really exists, it is theoretically possible that for therapeutic purposes the use of a combination of gland preparations might prove superior to that of one alone." As a matter of fact, combined extracts are often much more active

and render much more effective service than the same substances given singly. The experimental employment of such a combination has been carried out a number of times.

Woodwark[4] of St. Bartholomew's Hospital, London, relates his experiences with a combination of thyroid, thymus, pituitary, and adrenal. He used tablets containing 1 grain each of the four extracts in myxœdema, Mongolian idiocy, rickets, and obesity. Improvement was general, save that of the five cases of obesity only two improved, and one of the remaining three suffered from palpitation, evidently due to the medicine.* Elsewhere in this chapter will be found references to the work of others in this line.

"Kinetic Therapy."—If the postulates laid down by Crile in his "kinetic theory"[5] (see p. 38) are sound, and the "kinetic system" that he describes is a definitely correlated mechanism—and the author is firmly convinced of the fundamental soundness of this position—what can be more reasonable than a "kinetic therapy" based upon the tonic and regenerating powers of combined organic extracts? With regard to pluriglandular action, Ott[6] says: "Just as glands with an external secretion concur in taking up the work not accomplished by the others, and unite in the perfection of the products to be brought forth, in a similar way the glands with an internal secretion concur in the metabolites to be produced, a sort of physiological balance is maintained between the activities of the different glands in the wilderness of metabolism."

* The author believes that much of the good recorded in Woodwark's paper would have doubtless followed thyroid or pituitary-thyroid medication alone, especially in the cases with evident hypothyroidism. It is likely that the dosage of thyroid and adrenal may have been too large, and that the combination suggested is suitable only in cases where thyroid medication is indicated.

We can catch a glimpse from such statements as these of the power for good that a suitable combination of glandular extracts can be, in cases where half-speed function is common, and the decreased output of energy is not confined to the muscles, brain, nerves, or digestive glands, but also to the all-important hormone-producing organs.

It is quite reasonable that this form of medication should be extended to the treatment of many disorders in which the disturbance in the internal secretory organs may be seemingly negligible, but in which, however, there is a general decrease in the bodily activities, where it is right to suppose that the asthenic condition is not confined to the muscles, nerves, or elimination, but influences all the hormone-producing organs to the detriment of the whole system.

Amongst these must be classed many of those nervous diseases which are the bane of the general practitioner's existence, such as the "run-down conditions," neurasthenia, melancholia, and certain other insanities. It may be of advantage to collate a number of comparatively recent quotations from medical literature, which seem to give emphasis to the importance of the internal secretions in the causation and cure of these functional disorders.

The "Run-Down Conditions," etc.—Granting that the "guiding principle in therapeutics" stated previously is correct, it is clear that there are additional means whereby the deficient metabolism can be increased. The "change of air" is in itself a valuable tonic, but it is not always a convenient measure, and even if available, its influence can be enhanced by pluriglandular therapy.

In the so-called "run-down conditions," which include a large number of disorders of which no very definite

diagnosis can be made, as, for example, asthenia, neurasthenia, post-febrile conditions, convalescence, presenility, etc., there is of necessity a more or less obvious hypoendocrinism, which of itself is a serious matter. One cannot expect the internal secretory organs of the individual manifesting suboxidation, defective digestion, malassimilation, and the obvious evidences of being "run-down," to be working normally and supplying to the body the essential hormones which regulate practically the whole of its metabolic activities (see Chapter III.).

This hypoendocrinism is not only a symptom, it is also a serious factor in the further reduction of the forces of the body, for, as we have already seen, the protective substances involved in the cure of disease are presumed to be produced by the internal secretory organs.

This is a factor to be taken into consideration in all asthenic states. The encouraging results which follow the application of hormone therapy will amply repay one for the study and application necessary accurately to discern and treat these insidious but nevertheless important deficiencies.

The multiplicity of hormones and their potent influence on function prepare us for the conclusion that "many functional disorders are hormonically induced." It is obvious that the plasma normally contains many different hormones, and that if health is to be preserved, the supply of the hormones must be regulated with great nicety. "There is thus abundant opportunity for the plasma to become faulty in respect of its hormonic constituents; it may, *e.g.*, contain too little, too much, or a perversion of any one hormone, and these individual defects may be combined in endless ways, producing an endless variety of plasmic imperfections, each of which has its own peculiar effect upon metabolism. There can, indeed, be no doubt

that disordered hormonic function is responsible for numerous functional disorders. . . . Whenever disease is due to a hormonic or enzymic defect, the treatment obviously consists in correcting that defect."[7]

The Application of Pluriglandular Therapy.—The most important point to know, in applying these essentials in therapeutics, is what constitutes the most prominent element in the complex of hypoendocrinism. It is not always possible definitely to state which of the ductless glands is failing in its normal duties, nor can one measure the extent of the inactivity. Only by careful investigation of the minutiæ of the diagnosis can one gain an idea of the disturbance and its extent. At times it seems almost advisable to presume what cannot definitely be proved, and surely there are sufficient evidences of the hypoendocrinism, even though one cannot locate the principal secretory deficiencies.

There can be no doubt that the pituitary, adrenals, gonads, and thyroid are the principal endocrinous organs concerned in maintaining the vitality or tone of the body. Their influence upon muscular and vessel tone, on oxidation, and on the vital functions generally, are decidedly plus. Will the application of a mixture of extracts of these glands be useful, and if so, how are they to be combined ?

There is more than enough evidence to show that the empiricism which initiated pluriglandular therapy is well founded, as the evidence gathered here will show. The author is quite confident that this is a most effectual method of treatment.

In 1907 Rénon and Delille[8] described a " polyglandular syndrome," which is a prominent symptom-complex brought about by insufficient activity of several of the endocrinous organs. This corresponds to the term

"hypoendocrinism" used throughout this book. As far as possible they carefully differentiated the various deficiencies, and where certain signs suggested disorders of two or more organs, they gave corresponding pluriglandular extracts.

Sajous, in an editorial in the *New York Medical Journal*,[9] commenting on this field of study, says: "Cases of this class, which are steadily accumulating, show clearly that a vast field lies before us, sown with difficulties for the time being, but of immense promise for the future. . . . Its far-reaching meaning can hardly be overestimated, not only owing to the additional evidence it contributes in favour of the intimate relationship between various ductless glands and the vital process—*i.e.*, of oxidation and metabolism throughout the whole gamut of pathology—but also as an indication of the power of organic preparations when, in their therapeutical application, empiricism is replaced by rationalism."

The Relation of Hypoendocrinism to Neurasthenia.—The complicated conditions which are usually so indefinite as to have remained for years unnamed, the most important of which is termed "neurasthenia," because of the prominence of the nervous asthenia, must in a greater or lesser degree either be dependent upon, or at least associated with, disturbances in the hormone balance. We know that suboxidation, cell torpor, or deficient metabolism, is perhaps the most prominent factor in this class of cases, and if the nervous system, the muscular system, the digestion and metabolism in general, are working at low pressure, it is reasonable to suppose that the work of the internal secretory organs is equally deficient.

Lorand, in the Introduction to his book, "Old Age Deferred," states that neurasthenia is a disease which is

often based upon changes in the ductless glands, especially the thyroid, the sexual glands, and the pituitary body. The poor state of nutrition so often found in these persons is another manifestation of the endocrinous disorder, for, as Lorand reiterates, "in typical cases of this class there is a diminution of metabolism—*i.e.*, of the assimilation and conversion of food into energy. We shall have to think of the possibility of alterations in those organs which govern the process of metabolism . . .—the organs of internal secretion."

The frequency with which such conditions as amenorrhœa and impotence are found is conclusive proof that the gonads and their secretions are prominently concerned in the class of disorders which rightly or wrongly is called "neurasthenia." This also gives an idea of at least a part of the glandular extracts which are to be combined and used in its treatment.

Regarding the treatment of neurasthenia minor, Campbell Smith[10] emphasizes the need for steady and persistent treatment, and states that "for *a priori* reasons one would think that a similarly extended course of combined organic extracts would be very advantageous, and some recent reports of such a treatment of neurasthenia major and some forms of insanity tend to confirm this belief."

Starkey[11] has experimented with a combination of extract of thyroid, parathyroids, pituitary, ovaries, and testicles, and reports many encouraging results, giving his experience in the treatment of no less than 480 cases. The results obtained by him are briefly mentioned in the conclusion of his paper, which is as follows: "In conclusion, I think we may safely say that the polyglandular substance described herein has a marked stimulating effect, and that in acute asthenic conditions with low blood-pressure and suboxidation it activates the vital

process, and thus tides the patient over the most critical stages of the disease, while increasing the efficiency of his autoprotective resources. This is fully sustained by Sajous's views.

"The same polyglandular solution seems also to be almost a specific for neurasthenia. It has a marked stimulating effect on mental, nervous, and muscular activity, as well as on general metabolism and oxidation in general. It augments powerfully the contractile power of the cardiovascular system, and is therefore contra-indicated in cases of high blood-pressure. Finally, it increases the action of other drugs, arsenic, mercury, iodides, and salicylates in particular, and their curative efficiency."

It is particularly interesting to note that the administration of this pluriglandular substance by Starkey in a series of fifty persons in apparently normal health showed that the nitrogenous elimination was increased; they gained an average of 8 pounds in weight, following a short series of injections, they felt better, and their appetite, as well as their muscular and mental efficiency, was considerably increased. Sexual vigour was also augmented.

Practically as well as theoretically this medication has proved its importance, and it is predicted that the coming treatment of those conditions where function is diminished, due either to acute toxæmia as in fevers, or to the chronic toxæmias due to deficient metabolism, will be an attempt to supply some of the hormones that have been lost, and thus to restore the hormone equilibrium. Personal experience has convinced the author that the administration by mouth of a combination of glandular extracts* enhances the work of the whole

* For some years the author has been experimenting with various amounts and combinations of organic extracts. He has used a pluriglandular preparation quite like Starkey's, but made from glands more easily obtained, and in

system. The laboratory tests associated with such treatment have also demonstrated the increased capacity of the body to eliminate wastes, relieving the cells of not a little unnecessary toxæmia.

Tropical Neurasthenia or "Punjab Head."—It may be well to call attention to a common symptom-complex which is very closely allied to some of the conditions that have just been shown to be either due to or associated with hypoendocrinism. The majority of Europeans who live in the tropics eventually suffer from a combination of manifestations known as "Punjab head" or "Bengal head." This is, strictly speaking, a "run-down" condition, and the individual shows it by a change in his humour, a disinclination to accept responsibility, insomnia, and decreased power to concentrate. Often there are no evident organic disturbances, and the whole is set down as an attack of "liver."

Later, however, according to Sir R. Havelock Charles,[13] there develops a congeries of mental and sensory disturbances, generally accompanied by signs of defective metabolism. Moreover, such a condition of what is really a form of nerve exhaustion lowers the vitality and natural immunity or power of resistance to disease, and so renders the subject more susceptible to infection. This writer considers that the conditions of continuous residence in hot countries influence the nervous system of Europeans, both directly and also indirectly, by producing anæmia, imperfect metabolism, and affections of the alimentary and other systems. He finds an explanation of this in the old saying of Cuvier: "The nervous

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a more convenient form, as it may be given by mouth in capsules. This consists of a mixture of luteal and testicular extracts with the addition of small doses ($\frac{1}{10}$ to $\frac{1}{20}$ gr.) of thyroid and infundibular extracts. It has lately been put up in tablet form under the name *hormotone*, which was recently called a "*mitrailleuse*,"[12] but which is none the less effective.

system is at bottom of the whole animal, and the other systems are only to serve it."[14]

Cuvier evidently was wrong, for we now know that the sympathetic nervous system, and with it metabolism, oxidation, and resistance to infection, is definitely controlled by the hormones produced by the endocrinous organs. It seems most reasonable that the enervating climatic conditions of tropical countries have a specific and unquestioned influence upon the endocrinous organs, and tend to produce a hypoendocrinism which, in the author's opinion, is the fundamental cause of the neurasthenias of tropical origin.

Real value is given to this position by clinical evidence following pluriglandular therapy, and while the author has had no personal clinical experience in tropical countries, correspondents have mentioned the tonic influence of this method of treatment. It at least seems deserving of a much more extended trial, and doubtless will assume a more prominent position as the subject becomes better known.

Pluriglandular Therapy in Other Nervous Disorders.—Many facts which have been elicited in the study of the internal secretory organs indicate that numerous nervous disorders are the result of disturbances of the hormone balance. This has led a number of investigators to try various forms of organotherapy in their treatment, and without a doubt a valuable measure has been discovered in the administration of suitable combinations of extracts.

Delille and Vincent[15] relate encouraging results in the treatment of bulbo-spinal myasthenia. They found that a combination of the total extracts of the hypophysis and ovary effected a complete cure. This meant that the paretic manifestations of long standing disappeared, and the patient was able to walk. They found, however, that

the cure was not permanent, as the withdrawal of either one of the extracts led to a recurrence of all the symptoms; but as long as the pluriglandular medication was continued, the patient was seemingly quite well. This experience indicates the essential rôle of these internal secretions, and reminds one of the decided and specific influence of thyroid extract in myxœdema, etc.

Starkey[16] records good results from his pluriglandular treatment (see p. 42) in tabes. He writes: "Due to recent developments in organotherapy, we now have a gleam of hope, and I am satisfied that when this subject is better understood, many real cures of this disease will be recorded." He believes that this method "seems to fit very closely to the scheme of Nature in the use of these glands, the internal secretions of which have a profound effect on metabolism, increasing cellular activity and nerve tone."

He reports a number of successful cases from his records, the outline of one of which is sufficiently extraordinary to include here: "Case V. (exhibited before the Philadelphia County Medical Society, December 11, 1912). The patient, a lady, forty years of age, had been afflicted with tabes for twenty-seven years. Diagnosis had been made and confirmed by a number of eminent physicians from time to time. All this time she had complained of stabbing pains in the region of the stomach radiating down the legs. She had also girdle pains, Argyll-Robertson pupils, staggering gait, and inability to make quick short turns. The knee-jerk was not lost. She had been treated with potassium iodide, mercury, and morphine, or other hypnotics. She had also received *salvarsan* on two occasions.

"The family history was negative. Previous history: Had ordinary diseases of childhood, including measles.

No specific history. At age of thirteen commenced to have pain and spasms of legs, which were relieved by rest. This condition increased in spite of treatment, and at nineteen she began to have stabbing pains in stomach, eyes, and back. Double vision, lasting for several months, was present between twenty and twenty-one. These paroxysms of pain came at such frequent intervals as to be almost constantly present, and practically made her an invalid, confining her to her rooms.

"She first came to me on July 12, 1912, was examined, and received her first treatment the following day, and for four months has received injections twice weekly of my pluriglandular extract. At the present time she is entirely free from pain, and has been so almost from the first treatment. During the entire four months of observation she has had but one attack of pain, and that was mild in character, and due to over-exertion. She has received no other treatment, and has had neither sedatives nor mercury. At present I consider her cured and able to return to her family. She is now absolutely free from pain, has no ataxia in her gait, can walk a chalk line and turn corners sharply, stand with her eyes closed, and walk an average of three or four miles a day. She has also gained 12 pounds in weight. Her vision, which was nearly gone in the left eye, is now normal."

The "Jerry-built Constitution" and Hypoendocrinism.—The class of individuals who are far from normal and yet cannot consistently be called "defectives" has been considered by many to be congenitally deficient in the endocrinous activities. These individuals are sufferers from hypoendocrinism, and consequently "the vital stream flows sluggishly," and physically as well as mentally they are always below par. Most of these cases are congenital,

and have been given an excellent name—they are individuals with "jerry-built constitutions."

Jamin[17] of Heidelberg calls attention to the fact that frequently symptoms of chlorosis were noticed in young persons without the associated and characteristic alterations in the blood. He is convinced that it is probable that this disease, to which the name "juvenile asthenia" has been given, is due to endocrinous disorders, and is virtually an evidence of arrested development. He laid no particular emphasis upon which internal secretion was principally at fault, but without doubt here is another condition in which the use of organotherapeutic combinations eventually will prove useful. Boncour refers to a constitutional psychomotor asthenia in children, in which the patient suffers from a combination of motor debility, with marked muscular weakness and mental inertia and disability. He found that pluriglandular extracts had a marked influence upon the mental and physical development.

Dupuy[18] has made an extended study of the treatment of backward and defective children, and has used what he terms "*polyopothérapie endocrinienne associée*," and reports very encouraging results, which he summarizes as follows: (1) A rapid increase in stature, which had been slow to show itself with thyroid treatment, and a reduction in the rapid growth in those which seemed to be suffering from gigantism. (2) A less marked reduction in emaciation than with thyroid treatment alone, and a more decided tendency to regain the initial weight than when thyroid alone had been allowed. (3) An extraordinarily rapid modification of the urinary elimination, clearly indicating that metabolism is re-established on a more nearly normal basis and that assimilation has become regular. (5) A beneficial effect on the disorders due to

morbid phenomena, as well as on those lesions of a sympathetic character which are found in the backward (and which thyroid treatment often does not influence), including troubles in vision, incontinence, visceral ptoses, umbilical hernia, etc. (6) A general physical metamorphosis and a re-establishment of the sexual functions (menstruation, ovulation, etc.). (7) A psychic and sensory metamorphosis and a reduction of asthenia and excitability, as well as a noticeable progress in the intellectual capacity, thus allowing these unfortunates to take their proper place in society.

Quite often it is possible to augment the growth and the physical as well as mental activities of such individuals by suitable combinations of animal extracts.

The Ductless Glands in Mental Disorders.—It is not a very far cry from the jerry-built constitution to functional mental disorders, and again from the functional to the organic forms of insanity. Many papers of exceptional interest have suggested a relation between faulty internal secretory activity and various mental syndromes.[19] "Judging from the view-point of the general practitioner, at least, psychiatry—to which might be added its sister branch, neurology—does not afford as great a degree of satisfaction, in so far as therapeutic results are concerned, as do other specialities. An academic explanation of the morbid process supposed to be present in a given case is usually vouchsafed, but the results are in most cases disappointing. Modern researches, however, seem to be furnishing a clue to the cause of this unfortunate state of affairs. Defective anabolism through deficient oxidation and, conversely, imperfect catabolism of toxic wastes, have been known to explain many morbid phenomena of the cerebrospinal system, but the underlying cause of these departures from normal metabolism remained

obscure until the marked influence of the ductless glands upon these processes opened a new field of study."[20]

Sainton[21] is convinced that a large share of the etiology of mental disorders may be traced to pluriglandular insufficiency, and has shown that the proper application of combined opotherapy is often very helpful. He writes: "If the old adage, *Naturam morborum ostendunt curationes*, is true, one must admit that it is in a large degree due to the influence of the internal secretions in the pathology of mental alienation."

Dercum and Ellis,[22] holding the view that dementia præcox is associated with auto-intoxication, studied the pathology of the glands of internal secretion in eight cases of this disease. All the patients died of tuberculosis, a most interesting point in the pathology of dementia præcox. A striking finding was the underweight of the thyroid in seven of the cases. The adrenals also presented noted variations from the normal in weight and in size; the small amount of fat in their cortical cells was constant, probably indicating the diminished functional activity. These authors consider that "it is a remarkable fact that the almost universal cause of death in dementia præcox is tuberculosis, and if the feebleness to resistance to the tubercle bacillus is due to a fault of the adrenal system (pituitary, thyroid, and adrenals) we have reason to infer that it is one of the factors in the make-up of dementia præcox. The conclusion is not justified that an abnormality of the adrenal system is the cause of the mental symptoms, but our findings are at least in keeping with the inference that anomalies of the ductless glands exist in dementia præcox."

Bornstein,[23] from the results of his experiments during the past ten years, concludes that there exists a disturbed function of the sexual glands in dementia præcox, and

that the decreased function brings about a pathological mental exaggeration at puberty, and accordingly we have a disturbed metabolism which expresses itself in a psychic derangement. This coincides with the work of Abderhalden and Fauser, who found that the serum in dementia præcox decomposes sexual gland substances, and at the same time there is a disturbed function of the internal secretion of the ovaries and testicles.

Opotherapy in Hyposphyxic Conditions. — Martinet[24] describes an interesting circulatory syndrome—reduced tension with a diminution in the output of arterial blood, and a consequent venous stasis and general circulatory sluggishness—which he has called "hyposphyxia." This condition he finds to be invariably accompanied by hypoendocrinism, which may be advantageously treated by giving suitable pluriglandular extracts in conjunction with the physical and other means calculated to strengthen the circulatory function. Martinet finds that in these cases there is a digestive disorder which reacts upon the circulatory disturbance, and forms a vicious circle. He therefore treats it with secretin preparations, and at the same time augments the endocrinous dyscrasia by pituitary or adrenal extracts combined, as circumstances indicate, with thyroid and ovarian extracts. Excellent results were secured by this treatment of the hyposphyxia following acute infectious diseases, malnutrition, neurasthenia, and in the pretuberculous state. Improvement was even noted in congenital conditions in which this circulatory syndrome was prominent.

Prospects in the Pluriglandular Treatment of Cancer.— In Chapter III. the influence of certain of the interna secretions has been shown to be related to experimental cancer—certain transmissible tumours "took" better in castrated mice than in other animals. The relation of the

X ray to the activity of the endocrinous organs, and the possibilities of a connection between the artificially induced hypoendocrinism and cancer, are briefly mentioned in Chapter XXXI.

Cancer is essentially a disease of nutrition—*i.e.*, errors in nutrition, whether local or general, are the factors which permit of the implantation of cancer cells and the growth of the tumour. The ductless glands preside over nutrition. Hence it is not unreasonable to suppose that there may be some relation between disturbances of the hormone balance and cancer, and, too, that there may be some prospects of therapeutic value in the treatment of this disease by organotherapy.

As yet very little is known, but it seems that another door has just been opened a crack, and shortly we may expect to hear of some of the interesting things that lie just beyond that door.

At present there are three communications which show that this subject is receiving clinical consideration. Reference to these is made, not to "establish a new method of treatment," but to indicate the fruitfulness of this field of research, and perhaps to stimulate further consideration in this direction. Shirlaw[25] suggests the administration of a pluriglandular extract containing the extracts of the thyroid, adrenal, and hypophysis in their approximate normal proportions. The preparation in commerce, "*Tabloid Three Glands*," contains 6 grains thyroid, $\frac{3}{4}$ grain adrenal, and $\frac{1}{16}$ grain pituitary in each tablet. Shirlaw relates a case of pharyngeal carcinoma treated with this combination for two months, in which there was an obvious gain in weight and strength and an improvement in deglutition.

Bazzochi[26] has used a rather different pluriglandular combination for pyloric cancer. He prepared a fluid

extract of fœtal organs—thyroid, thymus, and spleen—which he injected on four successive days with immediate benefit. One year later the gain in weight amounted to 18½ pounds (8·5 kilogrammes), the health was good, and no trace of the tumour or suspicious symptoms remained. In this case the pathological examination of excised supraclavicular glands had shown the presence of typical epithelial nests.[27]

Previous to the above Billard[28] suggested the use of a combination of extracts of spleen, liver, and pancreas as an adjunct remedy in cancer. Its administration is not intended as an attempt to cure the disease, but was used by Billard to reduce the toxæmia and cachexia, and to increase the nutrition and general well-being. His reports were quite encouraging.

These suggestions, while somewhat divergent, are of peculiar interest, and, since practically no harm can come from the judicious application of pluriglandular therapy in cancer, may lead to other equally remarkable results.

The Administration of Antagonist Hormones.—It has been suggested that the administration of antagonizing hormone-bearing extracts is unscientific, and that the antagonism nullifies any possible therapeutic action. This may be true. It is certain that simultaneous administration of adrenal and pancreatic extracts shows the antagonism, since adrenaline glycosuria is controlled or not produced when the pancreatic extract is given at the same time.

It must be remembered, however, that the therapeutic action of hormones does not seem to be due so much to the replacing of the particular hormone in the economy (for the dosage must indeed be very small compared with the amount of the "chemical messengers" normally produced), as to its specific action upon the corresponding

hormone-producing cells—*e.g.*, a minute dose of thyroid serves a much broader purpose than could be ascribed to it *alone ;* it tends to cause the production of more of the thyroid internal secretion, and hence has a much wider influence. This is according to the axiom laid down by Hallion (see p. 24), and it can readily be appreciated that the action of small doses of antagonizing extracts serves to stimulate the corresponding organs, and thus to increase the hormone content of the blood—to strengthen the various "chemical messages" which are of such vital importance.

Another point worthy of emphasis concerns the capacity of the individual ductless gland to respond to such stimuli. It seems established that the degree of stimulation exerted by the administration of a hormone-bearing substance is in direct ratio to the need for such stimulation—*i.e.*, an extract is more efficient when the corresponding active principle is deficient in the body than when present in normal amounts. Hence in a combination of several extracts the principal action is the one which is deficient—that is to say, the more it is needed the more useful it is.

The "shot-gun" idea in hormone therapy is by no means so unscientific as some might think. In fact, it is quite possible that some of the failures following the use of a single animal extract may be obviated by combining it with one or more other synergistic extracts. This is particularly true of ovarian preparations (see Chapter XXIV., especially pp. 354–5).

"The internal secretory glands already unfold before the astonished view of the seeing eye a land of promise beside which the vast territories conquered by Lister and Pasteur are destined to pale into honourable insignificance. The ductless glands and their hormones come to us as peaceful conquerors who brook no denial. They lighten

our darknesses and show us miracles. In studying them and endeavouring to unravel their intricate and esoteric mysteries one seems ever and anon to be on the trail of the Great Secret, and in danger of losing one's mental perspective."[29]

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CHAPTER XXXI

THE CONTROL OF HYPERENDOCRINISM

The Use of Antagonist Hormones—Surgical Procedures—The Value of the X Ray—Röntgenotherapy in Exophthalmic Goitre—The Treatment of the Thymus in Graves's Disease—The Combined Treatment of Hyperpituitarism—The Reduction of Blood-Pressure by X-Ray Exposures.

HYPERENDOCRINISM, as contrasted with its opposite hypoendocrinism, is fortunately a much more infrequent condition, and clinically is not even a recognized entity. There are, however, a number of conditions due to the overactivity of certain endocrinous glands which already have been mentioned in the previous pages as occasion demanded. Some general principles may be gathered together in a short chapter upon the control of endocrinous overactivity.

The Use of Antagonist Hormones.—If a condition of hyperendocrinism is functional in character—that is to say, if there is no evident change in the structure of the affected organ—recourse may be had to the administration of hormone-bearing preparations that are known to have an opposing action to the secretion which, by its excess, is the cause of the trouble. This, we have seen, is occasionally possible in certain forms of Graves's disease by the administration of thymus extract; and adrenal extract was considered by Gibson[1] to be a remedy *par excellence* in this condition. In hyperovaria good results have been ascribed to the use of pituitary or mammary extracts,

and, more rarely, in hyperadrenia by recourse to pancreas preparations. In osteomalacia due to excessive ovarian activity, rather than mutilate the patient, Blair Bell[2] urges that pituitary and adrenal preparations should first be given a thorough trial.

Unfortunately, however, hyperendocrinous conditions are rarely functional, and the control of an organic change by the administration of antagonist hormones is not very satisfactory, although it is a sufficiently reasonable procedure to warrant its trial whenever feasible.

Surgical Procedures.—The surgical removal of offending organs, in part or wholly, has been practised for a number of years. Theoretically the results have been fairly good, although by no means as uniform as might be expected. Surgical interference, too, often goes farther than is best for the patient; for while overactive glands are a decided inconvenience, the absence of important organs is often of equal detriment to the maintenance of a physiological harmony. Ovariotomy is a most serious step, and total excision of these organs should only be resorted to in extreme cases and where absolutely necessary.

A combination of surgery and hormone therapy is occasionally useful, and it is quite common to remove a part of an enlarged thyroid, or to operate upon the skull to decompress the brain in pituitary disease, and supplement such treatment with organotherapy.

The Value of the X Ray.—Workers with the Röntgen ray have too often found out the remarkable antagonistic action that this physical power has upon endocrinous tissue. It may even be that the senile changes in the skin—that unhealthy, dried-up appearance which used to be so commonly seen in Röntgenographers—as well as the tendency to cancerous degeneration, is the result of an artificial hypoendocrinism due to the action of the

rays. It is certain that exposures to the X ray produce sterility, both in the male and female, and therapeutic use frequently has been made of this fact in the treatment of hyperovaria.

This method may be also used to reduce, rather than to suppress, glandular overactivity; and by careful dosage the results of the excessive secretion lessened without causing atrophy and the equally bad effect of entire absence of the hormones. Zimmern and Cottenot[3] have suggested that when a gland is in a state of functional overactivity, it is more sensible to the influence of the X ray, and that in such cases radiotherapy is particularly effective.

Röntgenotherapy in Exophthalmic Goitre. — There is considerable literature on the treatment of Graves's disease by means of X-ray exposures, and the reports are somewhat conflicting. It can be said that in general this treatment reduces the thyroid activity, but does not always do it sufficiently well or permanently. Murray[4] believes that " the application of suitable doses of X ray to the enlarged thyroid gland has in some cases proved to be of great value. The gland gradually diminishes in size, and the other symptoms subside. Atrophic changes in the secretory epithelium, and both interstitial and extracapsular fibrosis, appear to be induced by the action of the rays. . . . These changes are slow in development, so that the full effect of the treatment is not obtained until some months have elapsed. In favourable cases fifteen to twenty doses of the rays have been sufficient to bring about great improvement or practical recovery, but in others only slight improvement has followed a similar course of treatment. It is worth while to persevere with X-ray treatment for as long as a year if slow but satisfactory progress is being made. We have, more-

over, still much to learn of this valuable method of treatment."

The Treatment of the Thymus in Graves's Disease.—Persistence or hypertrophy of the thymus is quite a common finding in exophthalmic goitre, and since Capelle's[5] first reference to this subject, the literature carries the conviction that the thymus is concerned in this disease, and that hypertrophy of this organ is not simply a coincidence. Thymectomy is advised where the gland is demonstrable, but Lenormant[6] advises recourse to the X-ray treatment as a preliminary. Its elective influence upon the ductless glands may be of service, and reports are on record of the value of this treatment. If, however, little or no benefit is obvious, recourse to surgical removal of the gland is indicated, the field of operation frequently being extended to the thyroid.

The favourable influence of the Röntgen treatment of thymus hypertrophy is further emphasized by the report by Luzzati[7] of the successful treatment of two cases of thymic asthma in children. He considers that recovery may usually be induced by a prolonged course of treatment, and that the X rays may be used as a prophylactic in cases with the signs of latent thymic enlargement.

The Combined Treatment of Hyperpituitarism.—In hyperpituitarism, too, the X rays have been used, and occasionally have rendered good service. This has occurred sufficiently often to be convincing evidence that the rays have an action upon this gland similar to that which they exercise upon the ovaries or testes in spite of the intervening bone; but we are not destined to find so easily as this the means whereby such a condition may be controlled. Surgical measures are now often used, and are especially helpful in relieving the local

symptoms due to the pressure, and at times also by the removal of a portion of the gland.

Cushing[8] advises combining surgery and Röntgenotherapy, and has this to say of the value of such procedures: "In some of our more recent cases the results [of the X rays as a means of controlling the advance of a strumous hyperplasia] have been so encouraging as to justify a word in regard to this therapeutic adjunct to the operative measures. Certain observations show that in certain forms of hypophyseal tumour prolonged Röntgenization has a notable effect in ameliorating the neighbourhood symptoms. A widening of the constricted fields of vision serves as a reliable index of any diminution in the size of the struma. These results are explicable on the ground of the elective sensitivity of certain cells to the action of the Röntgen rays; and it would appear that neoplastic cells of epithelial type are particularly prone to undergo atrophy without inflammatory reaction under prolonged exposures. Hence, in view of the fact that the surgical measures at our disposal are merely palliative and directed toward neighbourhood symptoms alone, and in the case of an advancing struma are in no sense curative, it is possible that radiotherapy should often be employed as a supplementary measure. In several cases after almost complete blindness, vision has been restored under the combination of partial surgical removal of the struma and subsequent repeated exposures."

The Reduction of Blood-Pressure by X-Ray Exposures.—Presuming that hypertension is in many cases a result of hyperadrenia, Zimmern and Cottenot[3] have attempted to reduce excessive blood-pressure by exposing the adrenals to the X ray. The technique of their method is outlined in their paper and in a previous one,[9] which

was read before the Société de Biologie of Paris. They are convinced that material reductions (from 10 to 70 millimetres Hg.) of the tension are in this way made possible, and that this new application of radiotherapy is an effective and rational method.

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CHAPTER XXXII

MISCELLANEOUS EXTRACTS OF MINOR VALUE

Speculative Work with Animal Extracts—The Use of Extracts of Epithelium—An Extract of Heart Muscle—Bone Substance in Demineralized States—Ophthalmic Organotherapy

For the sake of completeness it may be well to mention certain other forms of organotherapy which are occasionally used, but the value of which is still quite problematic.

Speculative Work with Animal Extracts.—Doubtless the fundamental principle of organotherapy has caused a good deal of speculative clinical work to be done, and results which may have followed this work have naturally been credited to the treatment which was uppermost in the mind of the attending physician, while it is entirely probable that in many cases purely concomitant circumstances were responsible for any benefit that accrued. This is still the position of the sceptic in regard to nine-tenths of all forms of organotherapy.

Now that the science of the chemical correlation of the various parts of the body by means of hormones has been generally recognized, and the extremely complex condition of the body fluids is beginning to be appreciated, not a few prospectors in this vast field have presumed that not only the endocrinous organs *per se* are concerned in maintaining this balance, but, as Blair Bell has said, "it is probable that every cell of the body is a ductless gland, and has some influence on the life and functions of the

rest. But at present such a conception exists only as a dream in the minds of philosophical biochemists." Not a few physicians, especially in France, have attempted to materialize this dream. That they have done so in many instances is beyond question, as, it is hoped, previous chapters in this book have made clear, but it would seem that considerably more has to be learned and much supplementary work done before general use will be made of the several organotherapeutic preparations which will now briefly be referred to.

The Use of Extracts of Epithelium.—In France an occasional reference is found in books devoted to organic medication, as well as in the literature, to what has been called "cutaneous opotherapy." It is well known that keratin is prepared from epidermal substance, and, of course, is in regular use as a means of preventing the disintegration and absorption of drugs in the stomach which are given by mouth, and are intended to be principally active in the intestine. Zypkin has attributed therapeutic properties to this substance, and suggests that it prevents interstitial fibrosis following chronic inflammations of different organs.

Certain conditions in which there is a considerable involvement of the skin have been supposed to be benefited by treatment with extract of skin, and it has been applied following extensive burns and certain dermatoses, chief among which is the exfoliating form of dermatitis.

Carnot has suggested that preparations of skin might be used in burns, but, generally speaking, the therapeutic indications (the keratin coating of pills is hardly to be considered as a therapeutic agent) of cutaneous extracts are scarcely worth considering.

An Extract of Heart Muscle.—In myocardial disorders, where there is particular insufficiency of the heart muscle,

extracts of the heart itself have been recommended. These are said to have a restorative and tonic action.

Bone Substance in Demineralized States.—Preparations of bone are recommended in certain quarters as a means of recalcifying the system. They must, of course, not be confounded with bone marrow, which is a totally different thing.

Robin has put quite a scientific aspect upon the use of preparations of bone as a means of treating the deficiencies of calcium and mineral salts which are often associated with tuberculosis. The basis of this method is the fact that calcium salts of an organic nature are more easily assimilated and fixed by the tissues than the calcium salts in general use. In a communication by Brunet, in the *Annales de Thérapeutique Scientifique*, we read: "The only calcium preparations easily assimilated are those which are given in the food, and this explains why they are found in this organic form, because phosphates, carbonates, chlorides, and iron salts are absorbed by vegetable or animal tissues, and become a component part of their constitution. Thus, in the treatment of demineralized conditions, one should employ organic recalcifying bodies, and there is no other than powdered bone. The osseous tissue is the body's storehouse of calcium salts, and this store of calcium varies with the physiologic needs. In order to supply its lack of calcium, the body draws upon the reserve of salts in the bone, and in the assimilation of these salts nothing is lost, and the absorption by the tissues is complete, but, of course, this is a detriment to the bones—a fact which has been noticed frequently in disorders of calcium metabolism."

It is quite possible that the calcium and other salts which constitute the mineral part of bone are fundamentally different from those obtained by chemical

means. Much regarding this work has yet to be done. Suffice it to say that suitably prepared powders of bone are recommended as a means of supplying the specific lack in what is called the "demineralized states," and a number of prominent men, chief among whom is Professor Robin of Paris, have expressed their faith in this method of treatment.

Ophthalmic Organotherapy.—Last, and probably least, of the minor organotherapeutic agents are certain products of the eye itself. The ciliary body has been used in certain ophthalmic affections (principally irido-cyclitis), and even extracts of the crystalline lens of the eyes of young cattle have been used in Germany in the attempt to influence the onset of threatening cataract. It is stated that a course of such treatment has benefited vision, and caused an amelioration of the condition in the lens.

CHAPTER XXXIII

THE PREPARATION OF ANIMAL EXTRACTS FOR THERAPEUTIC PURPOSES

The Selection of the Fresh Glands—The Treatment of Excised Glands—The Preparation of the Extract—The Physical Form of Animal Extracts—The Present Methods of Standardization—The Estimation of Dose Units.

In the preparation of active, efficient organotherapeutic extracts several important points must be observed. There are not a few second-rate preparations on the market, and their use has not strengthened the position of "hormone therapy." The crude, old-fashioned methods of our ancestors no longer hold good. Scientific methods must be followed in order to obtain the highest degree of activity, as well as a definite standard thereof. Nomenclature, too, is in a most chaotic state.

The Selection of the Fresh Glands.—It need scarcely be said that everything depends upon the selection of the crude material, and experience has shown many points which make for more effective preparations, and therefore more satisfactory results.

The selection of the species of animal from which to secure the organ, the physical condition of these animals, their age, and even the state of certain physiological functions at the time of killing, are all evidently important factors. The species depends upon what organ is required; and it has become customary (though by no means an invariable rule) to take thyroids from sheep,

adrenals from sheep or calves, pancreas from cattle or pigs, ovaries from pigs or goats, testes from boars or guinea-pigs, etc. The physical condition of the animals must necessarily be good, and the optimum age naturally depends upon the glands desired. The gonads, for example, are secured from adults, the thymus from the young, and in some cases, as with bone marrow, the crude product is obtained preferably from the fœtus. In general, old animals in which development has ceased are not suitable, and the best preparations are made from the glands of animals in the height of development.

The relation of certain physiological states, such as the height of digestion or sexual excitement, the reaction to certain infections (as in the case of the spleen in tuberculosis—see p. 139), and pregnancy, must be also considered. Naturally it is desirable to secure an organ at a time when it is in a state of maximum activity or contains the largest possible amount of its active principles. Unfortunately, in practice this is not always an easy matter, especially when the manufacture is on a large scale.

The Treatment of Excised Glands.—After having selected the gland, it is cut out and very carefully freed from surrounding fat and tissue. Some have urged aseptic precaution in the recovery of the glands, suggesting sterile instruments, receptacles, etc. This seems hardly necessary, although, of course, cleanliness, not necessarily surgical, is essential.

In certain cases only parts of the organs are used. In the preparation of the most satisfactory ovarian products the corpus luteum is selected; in pituitary preparations the infundibulum is used; in the preparation of the adrenal principle the medulla is more suitable than the cortex or the whole gland, while the internal

secretion of the pancreas (the Langerhansian hormone) is naturally more abundant in that part of the pancreas where there are most islets—namely, the tail of the pancreas.

It is essential that foreign tissue be rejected, and this is especially true with extracts of such small glands as the parathyroids. This is a common stumbling-block to success in the manufacture of active products.

The Preparation of the Extract.—This is often a complex procedure, and is susceptible of many variations. The subject is too broad to receive more than passing mention, especially when its consideration is large enough to fill a book.*

The largest number and volume of preparations used in opotherapy consist of "total extracts"—*i.e.*, desiccated gland powder. Carnot considers it preferable, at least at present, not to attack the molecular structure of these organs by violent chemical procedures, but to utilize them as nearly as possible in their living condition.

The most satisfactory means of drying the pulp of animal substances is *in vacuo*. The rapidity with which this can be accomplished and the fact that the use of heat may be obviated make this the method *par excellence*. Choay, as a result of a most careful series of experiments in association with Gilbert and Carnot, and also many years of practical experience, states that "the method of choice is that which brings about an extremely rapid desiccation not only *in vacuo*, but without heat."

Choay's table—a part of which is included here—gives a very good idea of the average amount of water extracted in this manner, and that the averages are well

* See Choay* in "List of Books" (Appendix).

balanced is evident from the fact that the figures for pituitary, ovary, and thyroid are based upon the desiccation of 3,621 of the first, 8,863 of the second, and 9,012 of the last-named glands.

Organ.	Animal generally Used.	Percentage of Dry Extract.
Adrenal	Sheep	20
Duodenum	Pig	15
Hypophysis	Cattle	22
Kidney	Pig	20
Liver	Pig	30
Lung	Calf	20
Mammæ	Cow	20
Nerve	Pig	33
Ovary	Sow	16
,,	Cow	13
Pancreas	Pig	30
Parathyroid	Horse	22
Placenta	Ewe	14
Prostate	Horse	20
Spleen	Pig	23
Stomach	Pig	20
Testes	Bull	12
Thymus	Calf	17
Thyroid	Sheep	25
,,	Cattle	28

The Physical Form of Animal Extracts.—It has already been intimated that a very chaotic condition obtains in the present-day nomenclature of organotherapeutic products, and the exigencies of trade seem to militate against a satisfactory solution of the difficulty.

There are certain basic *forms* in which these preparations are put up:

1. The gland substance itself, fresh or preserved in syrup or confections. This form has all but gone out of general usage, as it is uncertain and inconvenient.

2. Dried and powdered glands—a common and convenient form, since they may be put up in suitable units as powders, tablets, cachets, and capsules. The suffix

ine has been suggested as a means of identifying this class (adrenaline, hepatine, etc.), but in the present state of affairs the suggestion is quite impossible of consistent application.

3. Gland substance powdered by trituration with an inert body (usually milk-sugar) "till extinguished"—*i.e.*, until an impalpable combination is made. This mixture is then divided into certain doses, which have a definite relation to the weight or number of the fresh glands. This is the usual method of the pioneer manufacture of organotherapeutic preparation.

4. The vacuum-dried gland, which has been treated by dissolving out, digesting, or otherwise removing certain substances which are nauseating, antagonistic to the normal physiological action of the product, or generally superfluous and unnecessary. In Germany the suffix *aden* has been used to indicate these repurified products (renaden, thyraden, etc.).

5. Extracts made by means of the usual solvents, chief among which are water, saline solution, and glycerine. These are used principally for hypodermic, and occasionally for intravenous, administration.

6. Basic substances prepared by complex chemical procedures and in the best state of purity. Frequently these are obtainable as salts of acid radicles (*e.g.*, adrenaline hydrochloride, hypophysin sulphate, etc.). They are put up in standard dilutions, and may be given by any of the usual methods.

The Present Methods of Standardization.—The better-known hormone preparations—adrenal, pituitary, thyroid—are generally physiologically and chemically standardized, although the accuracy with which one can standardize, say, adrenaline is not attainable in many other animal extracts. Products containing the active

principle of the adrenal glands, being in definite chemical form, are always standardized by their blood-pressure figure, and are the simplest of the ductless glands for standardization.

The activity of preparations made from the posterior lobe of the pituitary body is also estimated by animal experiment, as these preparations are valued by their blood-pressure-raising properties and by their power of contracting the isolated uterus. The estimation of the action upon blood-pressure is the method commonly adopted, but it is obvious that the action upon uterine contractility is the more useful, as the principal therapeutic use to which these preparations are put is on account of their power of contracting involuntary muscle.

The iodine coefficient is the present standard in the preparation of thyroid extracts; but it is by no means certain that the chemical standards are sufficient, and that the therapeutic effectiveness of two different extracts of thyroid, each conforming to the recognized standard, will be the same; for, after all, the activity of this preparation cannot be solely due to its iodine content. Beebe's method of securing the most active thyroid preparations has already been outlined in Chapter XIII.

The gist of numerous reports of experiments to determine the activity of several organotherapeutic preparations will be found in a valuable little book called "Physiological Criteria for Medicinal Substances."

Physiological tests on animals are now generally used by the more progressive manufacturers, and this seems to be a very wise and beneficial advance, although in this manner one can ascertain only in a very limited way the uniformity of the preparations. Still greater progress is anticipated in the near future, and much experi-

mental work is being done to bring the preparation of animal extracts to the highest possible plane.

The Estimation of Dose Units.—Practically all the preparations on the market are put up in definite doses. The ampoules contain a certain amount (usually 1 c.c. of a solution containing a definite amount of the active principle), while the tablets, capsules, and cachets are all supposed to represent certain uniform quantities of the various extracts. These amounts vary very little, and usually represent an average dose; hence the manufacturers, in a measure, are standardizing dosage. Their arbitrary quantities are invariably based upon clinical work, and thus facilitate the general application of this method of treatment, and obviate possible trouble in the early experiences of the physician with its application. It must be emphasized, however, that while the average dose of parathyroid or adrenal extract is invariably in milligrammes or fractions of a grain, and of spleen or liver extracts in grains or even grammes, the manufacturer's dose unit must be considered only as a unit of convenience, and not as a hard-and-fast standard.

As a matter of fact, the dosage of animal extracts is just like that of the alkaloids or any other drugs; the desired result should be the criterion, and enough should be given to accomplish this. Where one case will respond to a small dose, another may require many times the amount, and this fact proves a stumbing-block to many. They presume that the manufacturer's unit is the criterion, and are satisfied to give "two tablets three times a day after meals," instead of acquainting themselves fully with all the factors concerned—the disease to be treated, the minimum dose, its expected influence, and the evidences of reaction to the remedy—and then regulating

the dosage to fit the case, and using this treatment scientifically.

Even the makers of pharmacopœias have fallen into this common error. The British Pharmacopœia gives the dose of thyroid extract as "2 to 10 grains," when the average dose should be ½ grain or less. Indeed, in the case of a cretin, no definite dose can be laid down, except *quantum sufficit.*

CHAPTER XXXIV

THE LIPOIDS

What the Lipoids are—An Evident Detoxicating Action—Other Physiologic Activities of Various Lipoids—Iscovesco's Experiments — Homostimulants — The Adrenal Lipoids—A Lipoid from the Pancreas which stimulates the Liver—The Pituitary Lipoid—The Thyroid Lipoid—The Splenic Lipoid in Tuberculosis—The Lipoids obtained from the Gonads.

CERTAIN of the cells of the body, and particularly those which constitute the structure of the internal secretory organs, have been shown to contain a series of fat-like substances which may be extracted by means of organic solvents. These fatty bodies have been called "lipoids," and evidently have certain definite functions to perform. In a sense they are related to the hormones, for while there is no proof that they influence remote organs through humoral channels, they do exert, both experimentally and clinically, a decided homostimulant influence upon the organs to which they correspond.

What the Lipoids are.—From the researches of recent years, notably those of Iscovesco of Paris, we must conclude that the action of the lipoids in physiology is of such a character that it may be applied in therapeutics. As a matter of fact, it has even been suggested that the lipoids are none other than the active principles of the various animal extracts at present in fairly general use.

It must be remembered, however, that the term "lipoid" is a broad one, and that it covers all the sub-

stances that cannot be saponified as fats, but can be extracted by means of ether, chloroform, alcohol, acetone, etc. This includes the phosphatides, of which lecithin is the best-known example, and cholesterin, a very similar substance, which does not have a phosphorus molecule. Stepp has laid emphasis on the fact that the physiologic and therapeutic value of the lecithins is practically limited to those lecithins which are produced by the living organism to forward its own functional activities.

It is very clear, however, from the work of Iscovesco, that a number of additional lipoid-like substances—they are still called "lipoids"—differ from the better-known products of this nature (cholesterin, lecithin, etc.), and resemble much more closely the other active substances of the ductless glands; hence notice of them is taken in this book, and a brief résumé of our present knowledge of their action and value is given here.

An Evident Detoxicating Action.—Overton and Meyer were among the first to report upon the influence of certain of the lipoids upon poisons and toxins, and their early investigations showed that the lipoids have a soluble action upon narcotics. More recent work has amplified these observations, and Nerking and Reichert state that the administration of certain lipoids into the blood-stream thus diminishes or entirely eliminates the narcotic effect, and, even more important than this, that the lipoid content of various organs may be extracted or used up by means of the administration of narcotics or an excess of the toxins in the blood. This detoxicating action of the lipoids is of considerable significance in cellular physiology, and the fact that this capacity remains in the lipoids after extraction from the mother-cell-aggregate gives us another means of controlling cer-

tain conditions in which general as well as specific toxæmias are constant.*

Other Physiologic Activities of Various Lipoids.—The fact that lipoids are found in practically all the various cell collections of the body and in some of its fluids indicates in a measure their importance. It is necessary to emphasize the fact that they have absolutely no connection, either physically or chemically, with fats. In 1908 Iscovesco showed that the normal thyroid contained a series of lipoids, one of which had the remarkable property of provoking tachycardia with exophthalmos, and among numerous points since emphasized by this investigator is the fact that there undoubtedly are specific lipoids existing in each organ, some of which are antagonists and others synergists, and that by suitable means these useful lipoids may be extracted and used as a means of physiologically stimulating the organs in question. Then, too, antagonistic lipoids which may be present in animal extracts, thereby detracting from the desired physiologic action to be gained from their administration, may be removed by suitable solvents, and a more convenient preparation thus be obtained. This has been done in the case of thyroid extract, as referred to on p. 208.

Iscovesco's Experiments.—Most of the experimental work in this direction has been carried out by Iscovesco in the physiological laboratories of the Sorbonne in Paris. Generally speaking, the majority of the experiments consisted in injecting minute doses of preparations of this

* In Chapter XXI. reference is made to the detoxicating action of brain substance, which is one of the richest in lipoids of all the organs. The therapeutic action of lecithin and the cholesterins can only be mentioned in passing, as the limits of the scope of this book preclude a more extended study of the subject. For a concise résumé of the whole subject of lecithin, its physiology and uses, the reader is referred to "Merck's Annual Report," 1912, XXXVI., pp. 1–71.

character into rabbits, and continuing the treatment for varying periods. The various phenomena which appeared were carefully noted, and finally, after suitable periods, the animals were killed, and the different organs systematically examined, particular attention being paid to their respective weights. Control experiments with other animals, frequently of the same litter and always of the same age, weight, and sex, in identical conditions of life, were made. Details of these hundreds of experiments and the figures connected with them must manifestly be omitted, and only the essential deductions made, especially those which may have a therapeutic application.

An attempt was made to duplicate in man a number of the results of experiments made on animals, and as a result of this work a series of lipoid preparations have now become available in commerce.*

The Adrenal Lipoids.—From the cortex of the adrenal is secured a lipoid which provokes hypertrophy of the cortex of the adrenal glands, but exercises no influence whatever upon arterial pressure. It also excites the kidneys and liver very slightly, and possesses a peculiar stimulating action upon the hair follicles. Iscovesco refers to the use of this preparation in man in the following terms: "I have had occasion to try this preparation several times in man. When 2 to 5 c.c. are injected into the adult, the following three phenomena appear: (1) Marked acceleration of heart pulse, the beats increasing from 70 to 90 beats, and even more, in the first

* The "*Lipoïdes H. I.*" (homostimulant and for injection) cover practically the whole range of the ductless glands and other endocrinous organs, and are prepared in Carrion's Laboratoire de Biologie in Paris. The makers pertinently state that "the lipoïdes H. I. represent the active and specific substances of each organ, just as the alkaloids represent the specific substance of the plants." These preparations are dissolved in oil, the dose is standardized, and they are obtainable in ampoules.

two or three hours following the injection. This increase of the pulse is accompanied by a diminution of the arterial tension. These phenomena are variable, and disappear after a few hours. (2) Very frequently (in 60 per cent. of the cases) abundant perspiration is produced, which sometimes continues for twenty-four hours, and is usually nocturnal. I have thought that this phenomenon may be connected with that which I have previously referred to in regard to the stimulation of the growth of hair in my rabbits. This fact may also be an explanation of the nocturnal sweats of phthisis, which may be explained by a stimulation of the cortical part of the adrenals. (3) In cases where the adrenal cortex lipoid is given in daily doses of from 1 to 2 c.c., there is an increase of energy and a feeling of well-being which is particularly noticeable in the cachectic affections."

There is also another lipoid which is secured from the adrenal medulla. Its administration slightly stimulates these organs, but in a much less degree than the cortical lipoid. Further, this stimulation is confined particularly to the medullary portion of the glands, because in man this lipoid causes an increase of the arterial pressure and a reduction of the pulse. In animal experiments it has been found that injections covering a period of two months produce a decided influence upon the size and weight of the heart. The average weight of the controls was 2·69 grammes per kilo, while in the treated animals this average was increased to 3·80 grammes per kilo. Clinically, Iscovesco and others have used this medullary lipoid especially in tuberculosis, with the following results: (1) A decrease in the pulse and an increase of tension, which lasts twenty-four hours or more. (2) A decided feeling of well-being, which is particularly noticeable

in those cases of pulmonary tuberculosis accompanied by hypotension. (3) A much greater aptitude for work during the period of treatment.

It is interesting to note that further facts showing a relation between the lipoids and tuberculosis have been brought forward by Grinlew, who found in guinea-pigs that the lipoids in the cells of nearly all organs and tissues of the body undergo marked changes in tuberculosis. The aggregate of the lipoids and the phosphorus they contain is reduced in almost all organs, while the lecithin is decreased in all without exception. The organs which suffer most are the lungs, and next to these the spleen, cord, and liver.

A Lipoid from the Pancreas which stimulates the Liver.—It is of considerable interest to note that the principal physiologic influence of the pancreas lipoid is upon the liver. Its stimulating action upon the hepatic cells was remarkable. The average weight of liver in the control animals corresponded to 36 grammes per kilo, while after a series of injections of the pancreatic lipoid the average weight of the liver had increased to 47 grammes per kilo.

No other lipoids of the numerous ones examined influences the liver to such an extent. The increase in the liver seems to be quite normal, the tissue is not fatty, and there are evidences that the hepatic powers are augmented in proportion to the size of the organ. Experiences with the application of this pancreatic lipoid in man in doses of 1 to 2 centigrammes per diem reveals the following facts: (1) A very slight increase in blood-pressure. (2) A constant increase of weight. Its influence in diabetes is equally remarkable. The cases which have been considered divide themselves into two classes; in one the sugar increases considerably as a result of the injections, while in the other the glycosuria rapidly

diminishes and finally disappears. This seems to be a confirmation of the idea that certain diabetics are suffering from an essentially hepatic disturbance, while others are the results of pancreatic changes.

The Pituitary Lipoid.—The lipoid isolated from the anterior lobe of the pituitary seems to have the following properties: (1) It notably augments the appetite as well as the muscular activity. (2) It materially stimulates the kidneys, and augments not only the quantity of fluid passed, but also the urea and phosphates. (3) It does not act upon the weight of adults, but stimulates the growth of immature subjects. (4) It excites the adrenals, heart, and kidneys, but has no action on the genital organs, liver, or thyroid. (5) In man in doses varying from 2 to 5 centigrammes a day there is an initial increase in the pulse, later followed by diuresis and an increase in the appetite. In myasthenia a considerable increase in the muscular capacity follows its administration; while in myocarditis it has given relief by reducing pressure and rendering the heart beats more regular.

The Thyroid Lipoid.—Iscovesco has isolated from the thyroid a lipoid which strongly excites the adrenals, ovaries, uterus, and testicles. It also stimulates the heart, but curiously enough more in females than males. Its action was particularly marked upon the thyroid itself, which was also greater in females than in males. The action of this lipoid upon the growth of immature subjects seems to stimulate it slightly, but in adults it has the opposite effect.

The Splenic Lipoid in Tuberculosis.—It is believed that in the normal state there are certain substances that are capable of destroying the toxins of the tubercle and other bacilli. One of these, according to Iscovesco, is a lecithide

which he obtains from the spleen. This product, which is called *splenolecithide V.B.d.*, is said to have a specially favourable influence in the tuberculous. Its use by Iscovesco in 40 cases gave very good results in general, and this author suggests that this preparation exerts a valuable influence especially upon the active manifestations of tuberculosis, reducing tuberculous glands of the neck within a month, and generally increasing weight and resistance. It is given hypodermically in daily doses, and it is advisable to continue the treatment for two or three months.

The Lipoids obtained from the Gonads.—Three lipoid preparations have been secured from the gonads—*androcrinol*, the specific lipoid of the testicle; *gynocrinol*, the lipoid from the ovary; and *gynoluteol*, that from the corpus luteum. These all possess a stimulating effect upon the gonads, augmenting in a considerable degree the activity of the corresponding organs, as regards both actual growth and functional capacity. The testicular lipoid is used in conditions where the activity of the glands needs stimulation, as, for example, in infantilism and retarded growth, sexual neurasthenia, and impotence, and as a tonic in senility, especially when accompanied with hypertension and atheroma. It is usually given hypodermically in daily doses.

The ovarian lipoid has been used in conditions where the pelvic organs manifested aplasia, in the developmental troubles of puberty, including infantilism, sclerosis, and amenorrhœa. It has also been used in dysmenorrhœa, and is said to constitute a very valuable means of controlling painful menstruation. The luteal lipoid (*gynoluteol*) is more suited for the treatment of menorrhagia, and as a means of controlling the ovarian disturbances of pregnancy. It may also be used as a post-

partum remedy to favour uterine involution and lactation. It exerts in the artificial menopause a similar effect to that of lutein.

From the clinical and experimental facts at hand it seems established that the lipoids may even revolutionize the revolution which the introduction of the use of animal extracts into medicine is bringing about, as well as proving a means of enlightening us in a considerable degree regarding certain phases of endocrinous metabolism, and much credit must be given to those who have devoted so much time and effort to the investigation of this by no means well-studied subject.

CHAPTER XXXV

A GLOSSARY OF TERMS

A NUMBER of terms which are not generally used necessarily insinuate themselves into a book of this character. Many of them are not even found in late medical dictionaries, such, for example, as Dorland's seventh edition, published in September, 1913. These have been designated by a star (*). It has also seemed advisable to include the trade names of certain of the organotherapeutic specialities which happen to have been referred to in the text. These are printed in *italics*. Of course, the list cannot pretend to be complete. It is unfortunate that the nomenclature of this subject is being complicated by a vast number of coined words, each indicating a particular brand of the same preparation. Especially unfortunate is the indiscriminate use of trade names, such as *adrenalin*, *pituitrin*, etc., when these particular preparations are neither used nor meant.

Activator. A substance which changes a ferment from an inactive to an active form. Ex.: HCl activates pepsinogen as secreted by peptic glands to pepsin.

Adrenalin. The pressor principle of the adrenals, isolated by Takamine. The hydrochloride in 1 in 1,000 solution is used generally (Parke, Davis and Co., Detroit).

Adrenaline*. A name given to adrenal extracts, and generally adopted in British and French scientific literature, and not indicating any particular make.

Antihormone*. A chalone or antagonistic hormone; name given first to the internal secretion of the pancreas, because of its action upon the adrenal or chromaffin hormone.

Antithyroidine.* Moebius's serum from thyroidectomized goats, used in Basedow's disease (German).

Asthmolysin.* A mixture of adrenal and pituitary extracts, used in asthma. Each 1 c.c. ampule contains 0·0008 gramme adrenal and 0·04 gramme hypophysis and preservatives (German).

Autacoid* (Greek *αὐτός*, self, and *ἄκος*, a remedy). A generic term suggested by Sir E. A. Schäfer to include all the chemical messengers—*i.e.*, hormones and chalones (*q.v.*).

β-iminazolylethylamine*. A depressor and utero-stimulant amine prepared from histidine (and therefore also from intestinal extracts) by the action of putrefactive bacteria. Chemical name for *Ergamine* (*q.v.*). See also **Dépressine.**

Cephaline. One of the chemical constituents of the brain, quite similar to lecithin (and perhaps identical with it).

Cerebrin.* A proprietary dry extract of brain substance (Burroughs Wellcome and Co., London).

Cérébrine. A French proprietary analgesic containing coca, caffeine, and guarana. Nothing to do with brain preparations.

Chalone* (Greek *χαλάω*, I relax). A term suggested by Sir E. A. Schäfer to indicate the hormones which do not excite—the antagonistic hormones. Ex.: the "Langerhansian hormone."

Chemical reflex. Another term for "humoral reflex" (*q.v.*).

Choléine.* A proprietary form of repurified extract of bile in keratin-coated ovoids (Camus, Moulins, France).

Chromaffin. Staining with chromic acid or its salts. A term applied to the adrenal system and its hormone—*i.e.*, the chromaffin hormone.

*Cœliacin**. An extract of the mesenteric glands of sheep (E. Merck, Darmstadt).

Coenzyme. A substance which manifests a co-operative activity between an enzyme and some other non-colloidal substance. Ex.: the influence of bile salts on pancreatic lipase. The process differs from activation, for the combination is dissociable instead of permanent. A coenzyme can be separated from an enzyme by dialysis.

Coferment. Another term for "coenzyme."

Colloidogen*. A hypothetical substance which is presumed to be concerned in holding the minerals of the body in a colloid or organic state.

*Colloidogénine**. An extract of spleen, used by Bayle in tuberculosis, obtainable in syrup or dry powder (Chaix, Paris).

Crinogenic*, crisogenic*. Stimulating the production of secretions generally. (Should strictly be "criticogenic.")

D-quotient*. A term used in metabolic studies, indicating the relation between the urinary sugar and the urinary nitrogen.

Dépressine*. A crystalline depressor substance, prepared from intestinal extracts by Launoy and Œchslin (similar to, if not identical with, β-iminazolylethylamine, *q.v.*).

Endocrinous* (Greek ἔνδον, within, internal; κρίνω, I separate, set apart). Pertaining to the internal secretions. Occasionally written "endocrine." [Both words are philological monstrosities. In Greek a verb can be compounded directly only with a prep-

osition. All other parts of speech (ἔνδον is an adverb) form their derivatives from the corresponding noun of agency, in this case κρίσις, whose adjective is κριτικός, or from a verbal adjective, in this case κριτός (which has been set apart); hence the proper word would be "endocrito." When any part of speech other than a preposition is directly compounded with a noun of agency, the termination of the latter is changed to ια. The noun, therefore, should be ἐνδοκρισία. However, in deference to general usage, the word "endocrinous" is used throughout this book.]

Enterokinase. A ferment found in the duodenum, which is the activator of trypsinogen.

Enterokinesia*. The motor function of the bowels—peristalsis.

Enterokinetic*. An agent having an action upon the intestinal movements.

Epinephrin. The term given by Abel to the active pressor principle of the adrenal gland. Used erroneously by some to indicate all adrenal preparations, irrespective of their origin.

Ergamine.* A synthetic depressor substance, used as a uterine stimulant in hæmorrhage, etc. May also be isolated from intestinal extract (Burroughs Wellcome and Co., London). See also **Dépressine.**

Eusecrétine.* An autolized glycerine extract of scrapings of the gastric mucosa (Byla, Gentilly, France).

Ferment-precursor. See **Proferment.**

*Flavéine** (Latin *flavus*, yellow). An extract of the corpora lutea of pigs; made in France (Byla, Gentilly).

Gastrin. The gastric or pyloric hormone. Sometimes called "gastric secretin." See **Secretin.**

Gonads. The essential sex glands—*i.e.*, testes and ovaries.

*Hémato-éthyroidine**. Serum of thyroidectomized animals for use in Basedow's disease (Carrion, Paris).

Histotherapy (Greek ἱστός, tissue). A term rarely used instead of opotherapy (*q.v.*).

Holadin. A pancreas ferment preparation (Fairchild Bros. and Foster, New York).

Homostimulant*. A term used to indicate the particular action which organic extracts and lipoids exert upon the organs to which they correspond.

Hormonal. Zuelzer's "peristaltic hormone," prepared from the spleen of cattle (Schering, Berlin).

Hormone. A chemical messenger, which, formed in one organ, travels in the blood-stream to the other organs of the body, and effects a correlation between the activities of the organ of origin and the organs on which they exert their specific effect. Ex.: secretin (in duodenum) activates the pancreatic cell and changes the inert pancreatic protrypsinogen to trypsinogen, ready for use as soon as it reaches the intestine (and in this case further activated by enterokinase).

*Hormotone**. A tonic combination of hormone-bearing extracts, and used in hypoendocrinism and associated run-down states (G. W. Carnrick Co., New York).

Humoral reflex. The activity brought about through the blood and the hormone contents of its plasma (as compared with the nerve reflex).

Hyperendocrinism*. The opposite of hypoendocrinism; not, however, clinically known. (Should be hyperendocrisia; see note on **Endocrinous.**)

Hypoendocrinism*. Deficient internal secretory activity; usually refers to pluriglandular insufficiencies, as

special words (hypopituitarism, hypothyroidism, etc.) are applied to individual deficiencies. (Should be hypendocrisia; see note on **Endocrinous.**)

Hypophysin. The chemically pure posterior pituitary hormone, marketed as a sulphate (Meister, Lucius and Brüning, Hoechst-a.-M.).

Hyposphyxia.* A circulatory syndrome in which hypotension, venous stasis, and general circulatory sluggishness are present (Martinet).

Infundibulin. A term frequently used in the literature to indicate a standardized 20 per cent. solution of the active extract of the posterior lobe of the pituitary body.

Infundin.* The registered name for the "vaporole" infundibulin (*q.v.*) (Burroughs Wellcome and Co., London).

Kinase. A colloid activator which is of unknown composition. Ex.: enterokinase, which activates trypsinogen to trypsin.

Kinetic. Related to power or energy. The "kinetic system" (Crile) includes the brain, thyroid, adrenals, and muscles.

Kinetogenic. Producing motion—*i.e.*, causing growth.

Lipoid. A product of cell metabolism resembling fat, in that it is extractable with ether, chloroform, etc., and said to be similar in physiological and therapeutic action to the hormone-bearing organic extracts.

*Lipoides H. I.** A term used to indicate a series of lipoids isolated by Iscovesco, which are said to be *homostimulants injectables.* They are used for therapeutic purposes, and have a similar action to that of the corresponding glandular extract (Carrion, Paris).

Tab. Lutein. Extract of corpora lutea of the pig, each tablet representing 20 grains of fresh substance (Hynson, Westcott and Co., Baltimore).

Luteine.* A fatty pigment of a yellow colour, found in the corpus luteum. An extract of the corpora lutea made in Germany at the suggestion of Fraenkel.

Mammin. A preparation consisting of a sodium chloride extract of the udders of cows, freed from precipitable proteins (von Poehl, St. Petersburg).

Morphogenesia*. The production of growth.

Morphogenetics*. Substances producing growth—*i.e.*, having a trophic action. A term used by Gley in his consideration of hormones.

Motiline*. The enterokinetic principle found in extracts of the intestinal mucosa by Hallion and Enriquez.

Neohormonal.* The most recent preparation of the peristaltic hormone (Zuelzer) in solution from which all albuminous substances have been removed (Schering, Berlin).

Œstrus* (estrus). The period of sexual activity in animals; the "heat" or "rut."

Opotherapy (Greek ὀπός, a juice). A term introduced by Landouzy of Paris in 1895, indicating the use of animal extracts in therapeutics. In general use in France. Various other terms that have been used are "zomotherapy," "secretotherapy," "sequardotherapy," "animal therapy," and "organotherapy." The last of these is in quite general use in England and America.

Ovaradentriferrin. Merck's combination of ovarian substance (*ovaraden*) with nucleinate of iron in tablet form.

*Parathyroidine** (*Paratiroidina*). Vassale's active extract of the parathyroid glands (Italian).

Paratoxine. A petroleum-ether extract of repurified bile, containing cholesterin and the lipoids of bile. Especially recommended by Gérard and Lemoine in tuberculosis (France).

Parhormone*. Products of katabolism endowed with a physiological or hormone-like action (Gley). See **Ponogen.**

Peptocrinine*. A term suggested by Gley for a substance similar to secretin, which is extracted from the intestinal mucosa by means of a hot peptone solution.

Phosphatides. A class of lipoids which are esters of orthophosphoric acid. Ex.: lecithin.

Pituglandol. A solution of the active principles of the posterior lobe of the pituitary body (Hoffman, La Roche Chemical Works, Basle).

Pituitrin. A solution of the active principles of the posterior lobe of the pituitary body (Parke, Davis and Co., Detroit).

Pluriglandular*. A term used to indicate a form of compound glandular therapy—*i.e.*, the simultaneous administration of several extracts.

Polyglandular. A word of mixed derivation which should not be used. See **Pluriglandular.**

Ponogen (Greek πόνος, work). A cellular waste which may serve as a "chemical messenger" to influence some remote organ (Laumonier). See **Parhormone.**

Proferment. The substance in the glandular cell-unit which, after activation, becomes a ferment. Ex.: propepsin.

Progastrin*. The precursor of the so-called "gastric secretin."

Prosecretin. The precursor of secretin, found in the duodenal walls and changed or activated to secretin by hydrolysis with action of HCl.

Secretin. The typical hormone from the duodenal mucosa secreted as prosecretin, and later activated by HCl. (1) Pancreatic secretin: the secretin which activates the pancreatic cells; not secretin from the pancreas. (2) Gastric secretin: the secretin which activates the gastric cells. See **Gastrin.**

Secretogen.* An extract of the pyloric and duodenal mucosa containing the chief alimentary hormone—secretin (G. W. Carnrick Co., New York).

Sequardotherapy*. A little-used term for opotherapy (*q.v.*), based on the name of the " discoverer of animal therapy "—Brown-Séquard.

Sperminum. A definite chemical body obtained from the testicles, said to be a nerve tonic and cell stimulant (von Poehl, St. Petersburg).

Stagnin. An autolyzed, soluble extract of horse spleen, especially recommended in hæmorrhage (German).

Stimulin. A term sometimes wrongly used in the place of " hormone." Stimulins are, according to Metchnikoff, certain protective bodies in blood-serum, which produce immunity when inoculated by stimulating phagocytic action.

Suprarenin. An adrenal-medulla preparation (Meister, Lucius and Brüning, Hoechst-a.-M.).

Synthetic L-Suprarenin. The active pressor principle produced by chemical synthesis (Meister, Lucius and Brüning, Hoechst-a.-M.).

*Tabloid Three Glands.** A pluriglandular extract containing thyroid (6 grains), adrenal ($\frac{3}{4}$ grain), and pituitary ($\frac{1}{16}$ grain), suggested for use in cancer (Burroughs Wellcome and Co., London).

Testikulin. A proprietary extract of bull's testes, used as a general tonic and cell-stimulant (German).

Thymin. A proprietary extract of the thymus gland (von Poehl, St. Petersburg).

Thyratoxine.* A thyroid extract from which the toxic substances (lipoids, etc.) have been removed (Byla, Gentilly, France).

Thyroidectin. A product of the serum of thyroidectomized goats for use in Basedow's disease (Parke, Davis and Co., Detroit).

Thyroprotein. Beebe's nucleoprotein of the thyroid gland. An active thyroid extract (Parke, Davis and Co., Detroit).

Trypsogen. An extract of the pancreas, said to contain its internal secretion, in combination with adrenal inhibitory drugs for use in diabetes mellitus (G. W. Carnrick Co., New York).

Vasodilatin*. A hypothetical substance with a marked depressor action which is presumed by its sponsor, Popielski of St. Petersburg, to be present in extracts of all organs. This substance is also supposed to prevent the coagulation of blood.

Zymase. A soluble ferment or enzyme.

Zymogen. Another term for a proferment. The precursor of an enzyme; that part of the enzyme which is produced *in the gland.* Ex.: pepsinogen.

CHAPTER XXXVI

AN ORGANOTHERAPEUTIC DOSE-TABLE

Since the dosage and application of organotherapeutic products varies so greatly, it is difficult definitely to outline the therapeutic indications and the size of the doses to be given. The indications, as has been seen, are in many cases very numerous, and it does not seem advisable to give in the table which follows more than the most essential conditions in which the various animal extracts are available. The dosage, too, is purely suggestive, for it has been frequently stated that "there is no dose save dose enough."

An attempt has been made to indicate the class into which the application of this form of medication falls. It will be remembered that there are four distinct classes into which hormone therapy is divided:

1. **Substitution Therapy**: by the supply of a hormone to balance a definite loss due to disease or absence of an organ.

2. **Supplementary Therapy**: by augmenting directly or indirectly the so-called "humoral reflex," a presumed hormone deficiency resulting from an increased physiological demand, or from a decreased production of the needed principle. This includes the application of Hallion's law.

3. **Specific Therapy**: by causing a physiological action which is desired, though not as the result of any change in the hormone production.

4. **Empirical Therapy**: by applying hormone therapy in an unscientific, but nevertheless useful, manner, the origin of which many times was accidental, and the basis of which is not yet wholly explainable.

These four classes are numbered below in harmony with the numbers corresponding to each class mentioned above.

Unless indicated to the contrary, the doses mentioned refer to *grains of dried extract given by mouth*, and indicate the average *single* dose. It is given three or four times a day. Space prevents the use of both the English and French weights. The star (*) indicates that the dose may also be given hypodermically (in which case the standard solutions of the various substances are referred to); the dagger (†) that it is best administered intramuscularly; and the section (§) that it may be given intravenously.

This table is neither arbitrary nor exact, but merely suggestive.

Product.	Therapeutic Indications.	Average Dose.
		Grains.
ADRENAL .. (*total*)	Addison's disease[1]; hypoadrenia[2] (typhoid, cholera, acute fevers, etc.); osteomalacia[4]; rickets[4]; tuberculosis[4]; asthenia[2]; etc.	1–2
(*medulla*) ..	Hæmorrhage[3]; hypotension[2]; cardiac disease[4]; asthma[4]; poisoning[4] (strychnia, snake-bite, salvarsan, etc.).	1–3 min.*§
BILE ..	Liver insufficiency[2] (constipation, intestinal putrefaction, etc.); biliary stasis[2] (hepatic colic, gall-stone, icterus, etc.); muco-membranous colitis.[2]	2–5

Product.	Therapeutic Indications.	Average Dose.
		Grains.
DUODENUM (*secretin*)	Pancreatic insufficiency[2] (intestinal indigestion, steatorrhœa, etc.); gastro-intestinal insufficiencies[2]; diarrhœa[2] (especially in children in summer); diabetes mellitus[4]; constipation[4]; etc.	1–3
HYPOPHYSIS (*total*)	Acromegaly[2]; myocardial asthenia[4]; hypotension[2] (in typhoid, influenza, pneumonia, etc.); asthenia[4] (muscular, post-diphtheritic paralysis, etc.); obstipation[4]; etc.	½–5
INFUNDIBULUM	Obstetrics[3]; ischuria[3]; shock or collapse[3]; intestinal paresis[3] (meteorism, distension, etc.); diabetes insipidus[4]; amenorrhœa[2]; mammary flow[3] (breast abscess and insufficient milk); etc.	5–15 min.†§
INTESTINE ..	Dyspepsias[2]; constipation[2]; muco-membranous colitis[4]; enteritis[4]; etc.	1–3
KIDNEY ..	Renal insufficiency[3]; nephritis[2]; uræmia[2]; ischuria[2]; albuminuria[3]; etc.	3–5
LIVER ..	Hepatic insufficiency[2]; cirrhosis[2]; hæmorrhagic diathesis[4] (epistaxis, hæmoptysis, etc.); intoxications[2]; dermatoses[2]; diabetes[4]; etc.	10–25, 15–30 min.*
LUNG ..	Thoracic suppurations[4] (pleurisy, bronchitis, pulmonary abscess, etc.); tuberculosis[4]; etc.	2–5
LYMPHATIC	Adenoids[2]; hypertrophy of tonsils[2]; lymphatism[2]; Hodgkin's disease[2]; anæmia[4]; etc.	3–5, 3–5 min.†

Product.	Therapeutic Indications.	Average Dose.
		Grains.
MAMMÆ ..	Menorrhagia[3]; metrorrhagia[3]; fibroids[4]; agalactia[2]; hyperovaria[2]; etc.	
NERVOUS (*inc. brain and cord*)	Functional nervous disorders[2]; mental disorders[2]; neurasthenia[4]; certain organic nervous and psychic conditions[2]; etc.	3–5
OVARY (*cor. lut.*)	Menstrual disorders[2] (amenorrhœa, dysmenorrhœa, etc.); infantilism with genital underdevelopment[1]; climacteric disorders[1]; malnutrition[4]; neurasthenia[4]; etc.	3–5
PANCREAS ..	Intestinal indigestions[2]; diabetes mellitus[2]; tuberculosis[4]; infections[4]; etc.	2–5
PARATHYROID	Paralysis agitans[4]; tetany[2]; athrepsia[4]; epilepsy[4]; chorea[4]; exophthalmic goitre[4]; etc.	$\frac{1}{30}-\frac{1}{20}$*
PINEAL ..	Mental under-development[4]; defective metabolism[4]; etc.	3–10
PITUITARY	See Hypophysis and Infundibulum.	
PLACENTA ..	Agalactia[2]; uterine subinvolution[4]; etc.	3–5
PLURIGLANDULAR	Hypoendocrinism[2]; run-down conditions[4]; amenorrhœa[2]; neurasthenia[4]; malnutrition[4]; sexual neuroses[4]; insomnia[4]; cancer[4]; etc.	1–5, 2–10 min.†
PROSTATE ..	Prostatic hypertrophy[2]; prostatorrhœa[4]; prostatic neurasthenia[2]; etc.	1–3
SPLEEN ..	Tuberculosis[4]; malnutrition[4]; anæmia[2]; paludism[2]; splenomegaly[2]; typhoid[4]; etc. (see also Zuelzer's hormone).	2–8, 15 min.

Product.	Therapeutic Indications.	Average Dose.
		Grains.
STOMACH ..	Gastric insufficiency[2]; dyspepsia[2]; achylia; etc.	2–5
TESTES ..	Orchitic defects[1] (cryptorchism, infantilism, retarded growth, etc.); impotence[2]; senility[2]; asthenia[3]; neurasthenia[4]; functional neuroses[4]; adynamia; dermatoses[4]; etc.	1–3, 7–15 min.*
THYMUS ..	Exophthalmic goitre[2]; rheumatic arthritis[4]; rachitis[3]; early malnutrition[3]; etc.	5–15
THYROID ..	Hypothyroidism[1] (myxœdema, cretinism, infantilism, etc.); goitre[2]; minor hypothyroidism[2]; chronic rheumatism[4]; dermatoses[4] (ichthyosis, scleroderma, psoriasis, eczema, etc.); obesity[4]; migraine[4]; menstrual disorders[2]; insanity[4]; neurasthenia[4]; etc.	2–10, $\frac{1}{10}$–$\frac{1}{2}$
ZUELZER'S PERISTALTIC HORMONE	Intestinal paresis[3]; obstipatio chronica[3]; post-operative paresis[3]; etc.	10–20 c.c. †§

CHAPTER XXXVII

A LIST OF BOOKS ON THE INTERNAL SECRETIONS, ETC.*

THE list which follows comprises those books on various phases of hormone activity and therapeutics which are in the author's library, and which, with the current medical literature, have served as the basis for this work. The list, of course, does not comprise *every* book on this and allied subjects, although by far the largest majority are listed here. The arrangement of the list is made with the idea of giving prominence to the comparative usefulness of each book mentioned, and it seems that every really interested reader should have the first-named books in order that more definite information may be secured regarding the physiology and pathology of the ductless glands.

In order to save needless repetition, the references in the bibliographies to any among the following list of books have been made without giving the title of the book, and with simply a star (*) after the author's name, thus: "Biedl:* p. 52."

"INNERE SEKRETION: IHRE PHYSIOLOGISCHEN GRUNDLAGEN UND IHRE BEDEUTUNG FUR DIE PATHOLOGIE." † Von Professor Dr. Artur Biedl, Wien. Zweite neubearbeitete Auflage. 1913. Erster Teil. Pp. 534. Urban and Schwarzenberg, Berlin und Wien. M. 26. Zweite Teil. Pp. 692. M. 28.

* The books indicated thus (†) were added to the author's library after the body of this book was in type.

"THE INTERNAL SECRETORY ORGANS: THEIR PHYSIOLOGY AND PATHOLOGY." By Professor Dr. Artur Biedl, Vienna. With an Introductory Preface by Leonard Williams, M.D., M.R.C.P. Translated by Linda Forster. 1912. Pp. 586. John Bale, Sons and Danielsson, Ltd., London. 21s. net.

"THE INTERNAL SECRETIONS AND THE PRINCIPLES OF MEDICINE." By Charles E. de M. Sajous, M.D., LL.D. Sometime Professor in the Medico-Chirurgical College, Philadelphia; Knight of the Légion d'Honneur, etc. Fourth edition, 1911. Pp. 1873. 2 vols. F. A. Davis Co., Philadelphia. Stanley Phillips, London. £2 10s. net.

"INTERNAL SECRETION AND THE DUCTLESS GLANDS." By Swale Vincent, M.D., D.Sc., Professor of Physiology in the University of Manitoba. With a Preface by Sir E. A. Schäfer, F.R.S., etc. 1912. Pp. 464. Edward Arnold, London. 12s. 6d. net.

"THE DISEASES OF THE DUCTLESS GLANDS: FOR PRACTITIONERS OF MEDICINE AND SURGERY."† By S. P. Beebe, Ph.D., M.D. Professor of Experimental Therapeutics in Cornell University Medical College, New York. 1914. Pp. 400. Lea and Febiger, Philadelphia.

"MÉDICAMENTS ANIMAUX: OPOTHÉRAPIE." Par le Dr. Paul Carnot, Professeur Agrégé de Thérapeutique à la Faculté de Médecine de Paris. 1911. Pp. 602. Bailliere et Fils, Paris. Fr. 12.

"HORMONE THERAPY: 1913." By Henry R. Harrower, M.D., and Thos. Stephenson, F.C.S., F.R.S.E. 1913. *Prescriber* Offices, Edinburgh. 3s. 6d. Or Paul Hoeber, New York, $1.00.

"LEHRBUCH DER ORGANOTHERAPIE: MIT BERÜCKSICHTIGUNG IHRER ANATOMISCHEN UND PHYSIOLOGISCHEN GRUNDLAGEN."† Herausgegeben von Dr. Wagner v. Jauregg (Wien) und Dr. Gustav Bayer (Innsbruck). 1914. Pp. 516. Georg Thieme, Leipzig. M. 14.00.

"THE NERVOUS AND CHEMICAL REGULATORS OF METABOLISM." By D. Noël Paton, M.D., B.Sc., Professor of Physiology in the University of Glasgow. 1913. Pp. 217. Macmillan, London and New York. 6s., or $1.50.

"LIFE: ITS NATURE, ORIGIN, AND MAINTENANCE." By Sir E. A. Schäfer, LL.D., D.Sc., M.D., F.R.S., Professor of Physiology in Edinburgh. 1912. Pp. 36. Longmans, Green, London and New York. 1s. net.

"INTERNAL SECRETIONS FROM A PHYSIOLOGICAL AND THERAPEUTICAL STANDPOINT." By Isaac Ott, A.M., M.D., Professor of Physiology in the Medico-Chirurgical College of Philadelphia. 1911. Pp. 133. E. D. Vogel, Easton, Pa.

"ORGANOTHERAPY: OR, TREATMENT BY MEANS OF PREPARATIONS OF VARIOUS ORGANS." By H. Batty Shaw, M.D. Lond., F.R.C.P., Lecturer in Therapeutics, University College Hospital Medical School. 1905. Pp. 256. Illustrated. Cassell, London. 6s.

"SULLA ORGANOTERAPIA." Conferenzia Tentua il 27 Novembre, 1910. Dinanzi Alla Camera Medica di Trento. Per Professor Augusto Murri. 1911. Pp. 70. Zanichelli, Bologna. L. 2.50.

"DELL' OPOTERAPIA." Per Dr. Giuseppe Zingale. Estratto del Giornale *Medicina Nuova*. Roma. 1911. Pp. 92. L. 2.

"PRINCIPLES OF HUMAN PHYSIOLOGY." By Ernest H. Starling, M.D. Lond., F.R.C.P., F.R.S., etc. 1912. Pp. 1436. J. and A. Churchill, London. 21s. net.

"A TEXTBOOK OF PHYSIOLOGY: FOR STUDENTS AND PRACTITIONERS." By Isaac Ott, A.M., M.D., Professor of Physiology in the Medico-Chirurgical College of Philadelphia, etc. Third and revised edition. 1913. Pp. 911. F. A. Davis Co., Philadelphia. $3.50.

"HUMAN PHYSIOLOGY." By Professor Luigi Luciani, Director of the Physiological Institute of the Royal University of Rome. Translated by Frances A. Welby. In four volumes. Vol. II., "Internal Secretion; Digestion; Excretion; the Skin." 1913. Pp. 558. Macmillan, London and New York. 18s., or $5.00.

"LA PRATIQUE DE L'OPOTHÉRAPIE: PRINCIPES, INDICATIONS, POSOLOGIE." Par le Dr. L. Hallion, Directeur Adjoint du Laboratoire de Physiologie Pathologique des Hautes Études à Paris. 1911. Pp. 148. Masson et Cie., Paris. Fr. 2.00.

"LES PRODUITS BIOLOGIQUES MÉDICINAUX." Par P. Byla et R. Delaunay. 1912. Pp. 466. F. Gittler, Paris. Fr. 10.00.

"DES EXTRAITS OPOTHÉRAPIQUES: MODES DE PREPARATION, RENDEMENTS, POSOLOGIE." Par E. Choay, Docteur en Pharmacie de l'Université de Paris, etc. 1911. Pp. 180. Vigot Frères, Paris. Fr. 5.00.

"L'OPOTHÉRAPIE THYROÏDIENNE (THYROÏDE, PARATHYROÏDES, HYPOPHYSE)." Par le Dr. Gabriel Gauthier (de Charolles). Deuxième edition. 1913. Pp. 476. J. B. Baillière et Fils, Paris. Fr. 12.00.

"GLANDES SURRÉNALES ET ORGANES CHROMAFFINES." Par les Drs. M. Lucien et J. Parisot, Professeurs Agrégés à la Faculté de Nancy. 1913. Pp. 452. F. Gittler, Paris. Fr. 12.00.

"LA MÉDICATION SURRÉNALE." Par les Drs. Oppenheim et Loeper, Professeurs Agrégés à la Faculté de Médecine de Paris. 1904. J. B. Baillière et Fils, Paris. Fr. 1.50.

"THE PITUITARY BODY AND ITS DISORDERS." By Harvey Cushing, M.D., Professor of Surgery, Harvard University, etc. Pp. 450. J. B. Lippincott Co., Philadelphia and London. 18s., or $4.00.

"L' IPOFISI CEREBRALE FARINGEA E LA GLANDOLA PINEALE IN PATOLOGIA." Per Dr. Alfonso Poppi. 1911. Pp. 226. Paolo Neri, Bologna. L. 10.00.

"L'HYPOPHYSE ET LA MÉDICATION HYPOPHYSAIRE." Par le Dr. Arthur Delille. 1909. Pp. 336. G. Steinheil, Paris. Fr. 10.00.

"GLYCOSURIA AND ALLIED CONDITIONS." By P. J. Cammidge, M.D. Lond. 1913. Pp. 467. Edward Arnold, London. 16s. net.

"NEW ASPECTS OF DIABETES." By Professor Dr. Carl von Noorden, late Professor in the First Medical Clinic, Vienna. 1912. Pp. 160. John Wright and Sons, Bristol, 5s.; or E. B. Treat and Co., New York, $1.50.

"STUDIES CONCERNING GLYCOSURIA AND DIABETES." By Frederick M. Allen, M.D. 1913. Pp. 1179. Harvard University Press, Boston. $9.00.

"DIABETES: ITS PATHOLOGICAL PHYSIOLOGY." By J. J. R. Macleod, M.B., Ch.B., D.P.H., Professor of Physiology, Western Reserve University, Cleveland. 1913. Pp. 224. Edward Arnold, London.

"THEORY AND PRACTICE OF THYROID THERAPY." By Herbert Ewan Waller, M.R.C.S. (Eng.), L.R.C.P. (Lond.), etc. 1911. Pp. 154. John Bale, Sons, and Danielsson, London. 5s. net.

"DISEASES OF THE THYROID GLAND." By George R. Murray, M.A., M.D., F.R.C.P., Professor of Medicine, Victoria University, Manchester. 1900. Pp. 112. H. K. Lewis, London. 7s. 6d.

"NOUVELLES ÉTUDES SUR LA PHYSIOPATHOLOGIE DU CORPS THYROÏDE." Par les Drs. Léopold-Levi et H. de Rothschild, Lauréats de l'Académie de Médecine de Paris. Second edition. 1911. Pp. 558. O. Doin et Fils, Paris. Fr. 10.00.

"LA PETITE INSUFFISANCE THYROÏDIENNE ET SON TRAITEMENT." Par les Drs. L. Levi et H. de Rothschild. 1913. Pp. 309. O. Doin et Fils, Paris. Fr. 5.00.

"CONTRIBUTION SUR L'ÉTUDE DE L'OPOTHÉRAPIE MAMMAIRE." Par le Dr. M. Luncz de la Faculté de Médecine de Paris. 1911. Pp. 136. Vigot Frères, Paris. Fr. 4.50.

"LES PARATHYROÏDES." Par Dr. Louis Morel. 1912. Pp. 334. A. Hermann et Fils, Paris. Fr. 10.00.

"ÉTUDES D'ENDOCRINOLOGIE." Par Dr. Naamé de Tunisie. 1913. Pp. 72. A. Maloine, Paris. Fr. 1.50.

"LA SÉCRÉTION PANCRÉATIQUE." Par Emile F. Terroine. 1913. Pp. 133. H. Hermann, Paris. Fr. 5.00.

"CONTRIBUTION A L'ÉTUDE DU MÉCANISME DE LA SÉCRÉTION EXTERNE DU PANCRÉAS." Par Dr. A. Hustin. 1913. Pp. 101. Impr. Vaillant-Carmanne, Liége.

"KLINIK UND BIOLOGIE DER THYMUSDRÜSE." Von Dr. H. Klose und Dr. H. Vogt. 1910. Pp. 200. Laupp'schen Buchhandlung, Tübingen.

"LEÇONS SUR LA LITHIASE BILIAIRE." Par Dr. A. Chauffard, Professeur du Clinique Médicale à la

Faculté de Médecine de Paris. 1914. Pp. 244. Masson et Cie., Paris. Fr. 9.00.

"LES SÉCRETIONS INTERNES: LEUR INFLUENCE SUR LE SANG." Par Dr. M. Perrin, Professeur Agrégé à la Faculté de Médecine de Nancy. Préface de M. le Professeur Gilbert. 1910. Pp. 147. J. B. Baillière et Fils, Paris. Fr. 4.00.

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"ADRENALIN: ITS PROPERTIES, PHYSIOLOGICAL ACTION, AND THERAPEUTIC HISTORY." 1912. Pp. 104. Parke, Davis and Co., Detroit and London.

"MANUEL DE L'OPOTHÉRAPIE." Publié par le Laboratoire Chaix. Pp. 98. Chaix et Cie., Paris. Fr. 0.50.

"ÉTUDE PHYSIOLOGIQUE ET CLINIQUE DES GLANDES À SÉCRÉTION INTERNE." Par Dr. Albert Fournier. 1912. Pp. 120. Fournier Frères, Paris

"THE TRANSFUSION OF LIFE." By L. H. Goizet, M.D. Translated into English by E. Montépic. 1912. Pp. 191. Richter and Co., London.

"LA TRANSFUSION VITALE." Par Dr. L. H. Goizet de la Faculté de Médecine de Paris. 1912. Pp. 319. Richter et Cie., London.

"RATIONAL ORGANOTHERAPY: WITH REFERENCE TO UROSEMIOLOGY." By Professor Dr. A. von Poehl and others. Translated from the Russian. 1906. Pp. 239. J. and A. Churchill, London. 7s. 6d. net.

"ORGANOTHERAPEUTISCHES COMPENDIUM." 1912. Pp. 116. Prof. Dr. v. Poehl and Söhne, Berlin, etc.

"PHYSIOLOGICAL CRITERIA FOR MEDICINAL SUBSTANCES." 1913. Pp. 59. Burroughs Wellcome and Co., London.

"TRAITEMENT DE LA TUBERCULOSE PAR LA PARATOXINE BASÉ SUR L'ACTION ANTOTOXIQUE DU FOIE." Par Drs. E. Gérard et G. Lemoine, Professeur du Clinique Médicale à la Faculté de Médecine de Lille. 1908. Pp. 74. Vigot Frères, Paris. Fr. 1.50.

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