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the 1990s, the number of people in the UK who are aged 65 and over has increased from 10.5 million to 13.5 million (19.5% of the population).

There is a growing awareness of the need to address the needs of older people, and the Government has set out a strategy for the 21st century in the White Paper on *Ageing Better: The Government's Strategy for Older People* (Department of Health 1999). This strategy is based on the following principles:

- Older people should be able to live independently and actively in their own homes.
- Older people should be able to live in their own communities.
- Older people should be able to live in their own homes and communities for as long as possible.

These principles are underpinned by the following objectives:

- To ensure that older people are able to live independently and actively in their own homes.
- To ensure that older people are able to live in their own communities.
- To ensure that older people are able to live in their own homes and communities for as long as possible.

The White Paper also sets out a number of key actions to be taken to achieve these objectives. These include:
 

- Improving the quality of care in residential care homes.
- Improving the quality of care in care homes for people with dementia.
- Improving the quality of care in care homes for people with mental health problems.

The White Paper also sets out a number of key actions to be taken to improve the quality of care in care homes. These include:
 

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- Improving the quality of care in care homes for people with mental health problems.

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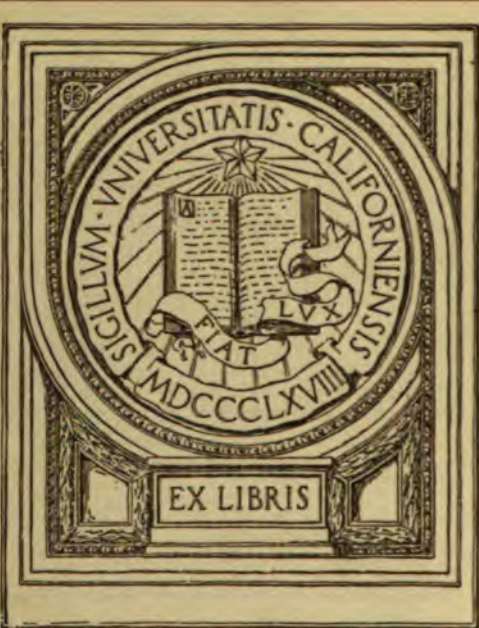
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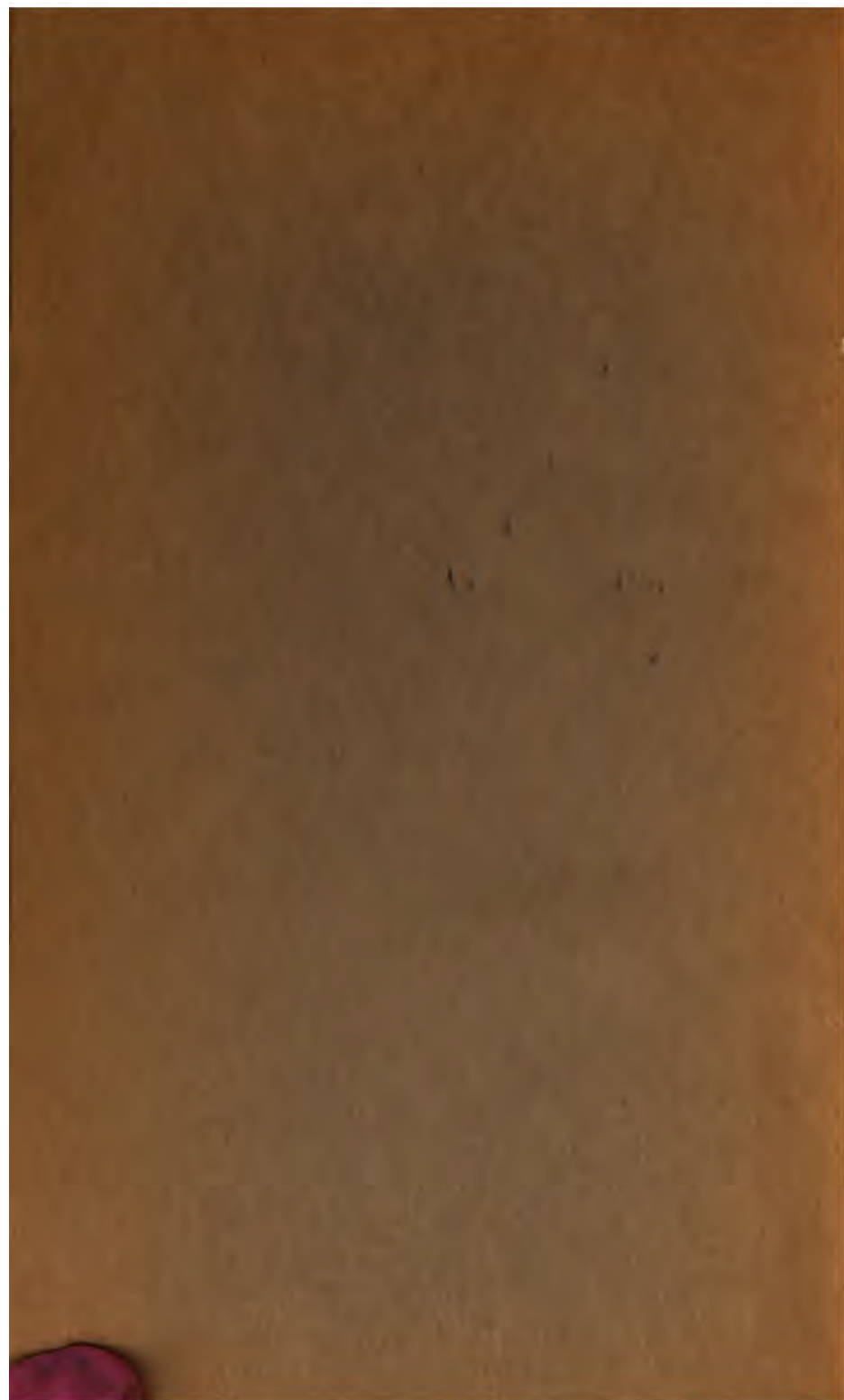
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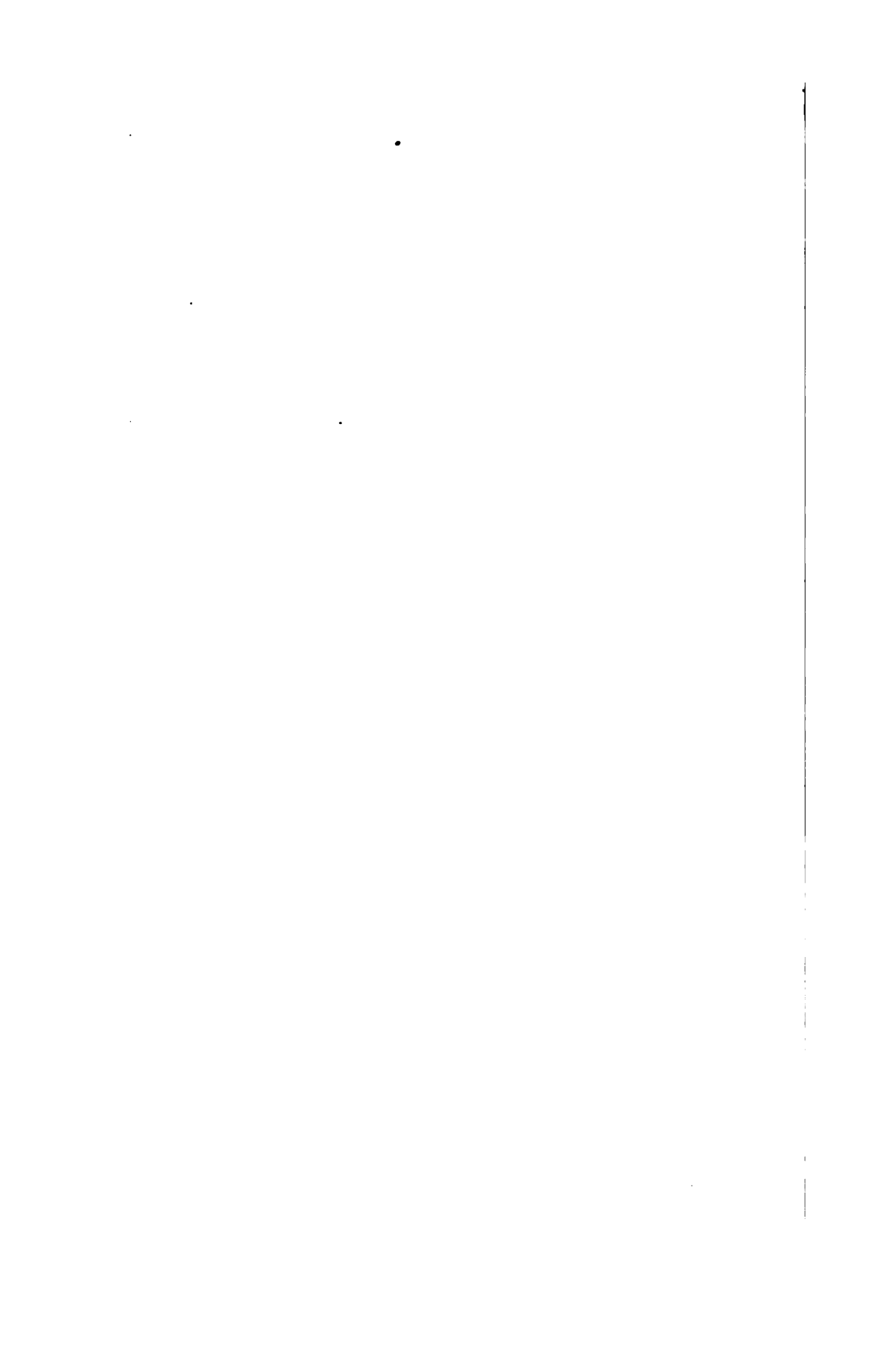
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# INTERNAL SECRETION-

## AND THE

# DUCTLESS GLANDS

BY

SWALE VINCENT

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WITH A PREFACE BY

PROFESSOR E. A. SCHÄFER, F.R.S.

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1912

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## PREFACE

By PROFESSOR E. A. SCHÄFER

“GOOD wine needs no bush.” The contents of the present volume speak for themselves ; they need no eulogy from me.

Almost all we know regarding the internal secretions is the product of the last twenty or five-and-twenty years ; prior to that our information regarding the functions of the ductless glands was a blank, enlivened by all kinds of conjectures. Now the subject requires more than 400 pages even for a concise digest of the accumulated facts, and some 3,000 references to deal with the literature. No doubt there are still plenty of gaps to be filled—some of them wide and deep. Nevertheless, it is wonderful what an amount of knowledge of these bodies—formerly so mysterious—has been piled up within a short period. They are, indeed, better understood than some organs the functions of which have been the object of investigation ever since physiology established itself as a science.

There always comes a time in the progress of knowledge of a subject, especially if that subject be a new one, when it is desirable that investigators should have an authoritative work of reference in which the history and literature are adequately dealt with ; if only to ascertain the exact position of the milestones on the road the investigator is himself preparing to travel, and the direction of the side-roads leading off from it. This is what Professor Swale Vincent has furnished us with, and in doing it he has

laid us under a debt of gratitude. No one who has not had the experience can understand the hopelessness of the situation with which a worker is confronted in his first attempt to ferret out for himself, from innumerable journals, the literature of the particular problem which is interesting him. For the subjects herein dealt with much of this labour will now be spared him.

To those teachers and students who want precise, recent knowledge regarding an interesting chapter in physiology the book is no less necessary than to the investigator. And it appeals to a third and wider circle—those who are engaged in the practice of medicine; for its subject is of no less importance from the clinical and pathological than from the physiological point of view. In numerous instances abnormalities in the bodily functions prove to result from disease of the ductless glands or from perversion of their secretions. It therefore follows that no medical man can afford to remain ignorant regarding these organs. Professor Swale Vincent's book removes all excuse for such ignorance.

## AUTHOR'S PREFACE

I MAKE no excuse for offering this work to my medical and scientific colleagues. The subject with which it deals has occupied a large share of my time and energy for more than fifteen years.

There are some portions of the book which are necessarily of the nature of compilation, but upon most of the subjects treated I have obtained first-hand information, and have published the results in various scientific journals. On other subjects many confirmatory investigations have been made throughout the preparation of the present work, and these find their expression in the attitude adopted, whether adversely critical or otherwise, towards previous investigations.

I am aware that the work has many defects. It is to be feared that some important papers may have escaped notice. The literature of the various branches of the subject is now of enormous dimensions, and when it is remembered that the topics treated may be dealt with in journals ranging over the whole realm of medicine, as well as those of anatomy, physiology, chemistry, and general biology, perhaps some leniency may reasonably be expected in this regard. I have further to plead that library facilities in Winnipeg are yet very inadequate, and that during the summer of 1910, when I had expected to avail myself of the opportunity of working in the London libraries, I was laid aside with illness for several months.

The main outlines of the present work have been previously published in German in the *Ergebnisse der Physiologie*, and



I have to thank the editor, Professor Asher, of Bern, and the publisher, J. F. Bergmann of Wiesbaden, for their courtesy in allowing me to use the material of my two contributions to the *Ergebnisse* as the basis of the present book.

The illustrations are mostly derived from papers contributed to various journals from time to time, either by myself, or by or in conjunction with pupils and others working under my direction. A large number have been drawn for me by Mrs. F. D. Thompson, whose histological knowledge and artistic skill have been generously placed at my disposal, and to whom I have to offer special thanks. The figures which Mrs. Thompson has specially drawn for the present work are Nos. 13, 14, 30, 38, 39, 48, 86, 87-89, 92, and 93; while Nos. 10-12, 49, 73, 75-77, 82-84 were drawn by her to illustrate her own paper in the *Phil. Trans.*, or papers published in conjunction with myself.

The tracings have been for the most part taken from papers by myself, or conjointly produced in the *Journal of Physiology*, and I have to thank Professor Langley for supplying clichés of blocks of many of these. Some of the tracings have, however, been taken from the records of recent class demonstrations (Figs. 40-44), or from unpublished work in my laboratory (Fig. 47). Figs 49A and 49B were drawn by Mr. Carmichael from sketches kindly furnished by Professor Evatt, of the Manitoba Medical College. Figs. 45 and 46 were drawn under my direction by Mrs. Thompson.

Two drawings only—viz., Diagrams *A* and *B* of Fig. 74—are copied from another author. These are taken from a paper by Dr. Kohn, of Prague.

I have to thank Mr. A. T. Cameron, Lecturer in Physiology in the University of Manitoba, for much assistance, bibliographical and otherwise, and Mr. Charles H. O'Donoghue, of the Zoological Department, University College, London, for reading through the manuscript of the section on Ovary and Corpus Luteum, and for microscopical preparations of the

ovary of *Dasyurus viverrinus*, from one of which Figs. 13 and 14 have been drawn.

To Dr. Cramer of Edinburgh I am indebted for assistance and criticism in the chemical portions of the book; and to Dr. Leonard Kidd for his kindness in sending me some references to literature which might otherwise have escaped my notice.

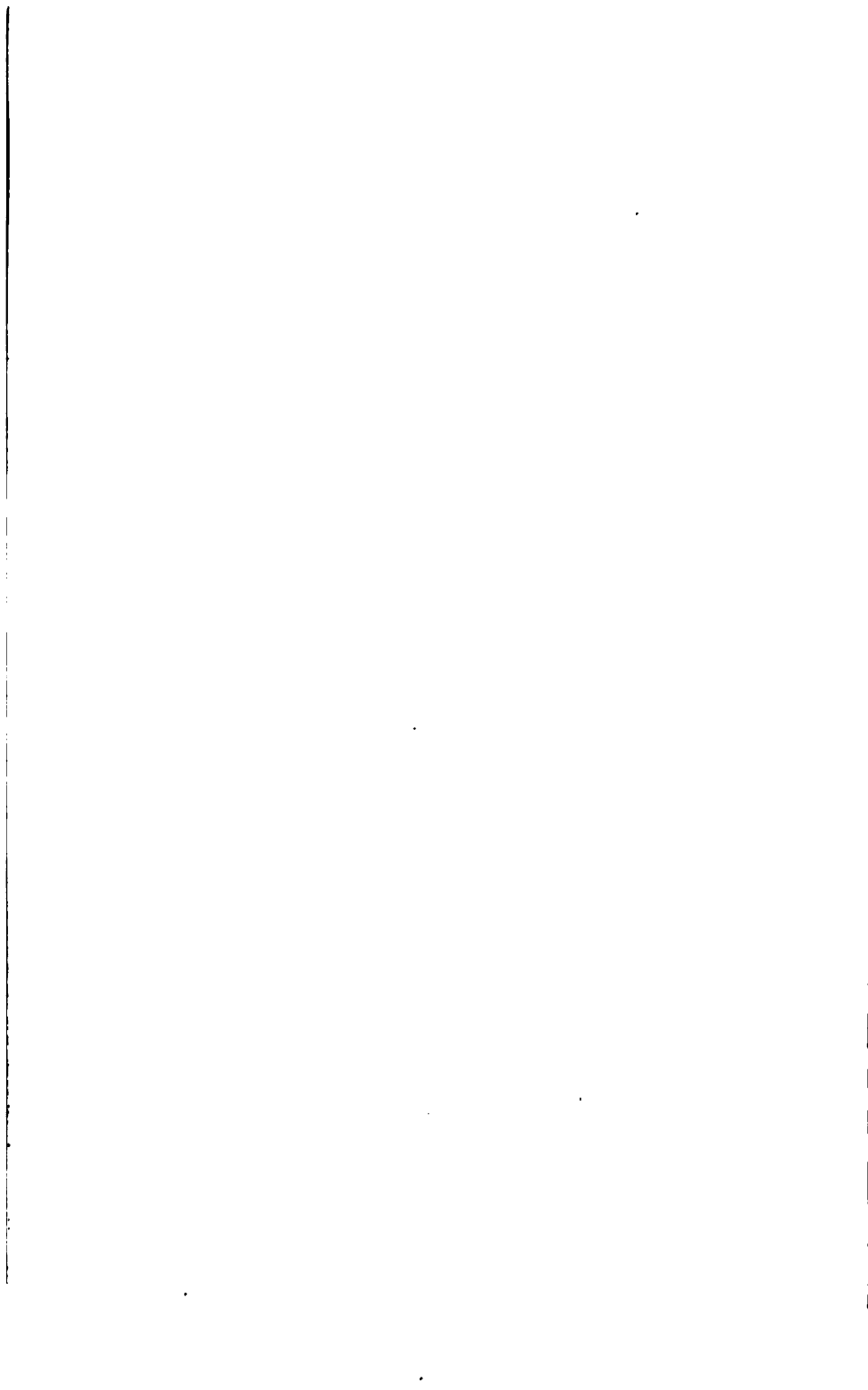
Some tables have been taken from Biedl's book on "Internal Secretion," published in 1910.

I owe a debt of gratitude to Professor Schäfer for his kindly encouragement and advice on various matters extending over a period of many years. From the time when I had the privilege of acting as his assistant in University College, London, he has always been ready to place the resources of his laboratory at my disposal, and to assist me in numerous other ways.

Finally, my thanks are also due to Mr. Edward Arnold for his courtesy and kind consideration to myself during the preparation of the book. My illness has delayed the publication for a year.

SWALE VINCENT.

LONDON,  
June, 1912.



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# INTERNAL SECRETION AND THE DUCTLESS GLANDS

## CHAPTER I

### INTRODUCTORY—SECRETION AND INTERNAL SECRETION

DURING the last twenty years a vast amount of investigation has been carried out upon the subject of internal secretion, and very numerous facts have been ascertained and various theories put forward. Our knowledge of the subject is still in many directions very indefinite, and it will be my duty to adopt a somewhat more sceptical and less optimistic attitude in regard to certain branches of the subject than has been taken up by some modern writers. It is desirable, at any rate, that the material should be collected and critically examined, though the task is rendered difficult from the fact that many of the contributions are to be found in obscure and even inaccessible publications.

Before passing on to the discussion of *internal* secretion, it will be well to define as accurately as possible our conception of secretion in the most general sense of the word. In plants as well as animals, in unicellular as well as in multicellular organisms, various substances are formed as a result of the metabolic activities of the living protoplasm. In the unicellular organisms these substances help in the absorption of food material, or serve some other purpose in the economy of the cell, or they are cast away as waste materials into the medium in which the creature lives. In multicellular organisms the materials may be utilized either in the cell itself or in some other parts of the body. In the latter case they may be of service either to minister to the proper function of some special apparatus (such, for example, as

the digestive tract), or are essential to the integrity or the general functions of the entire organism. On the other hand, they may be of no further use in the economy, and may be cast out as waste products.

By the term "secretion," applied in its most general sense, is, or has been, understood the separation out of a substance or of substances from or by the agency of the living protoplasm. This, the original conception of the process, has long been extended to include also the preliminary preparation, or a more or less complete elaboration of the materials which are supplied by the processes of osmosis and diffusion, and in the case of the multicellular organisms by the blood circulating through the organ or tissue.

Johannes Müller (258) pointed out that the whole process of secretion consists of two phases—the production of certain materials and the casting out of these materials upon a surface either in the interior or upon the exterior of the body. The first phase he called "secretion," the second "excretion." In some cases the material eliminated might be found in the blood-stream, and was simply separated by the cells of the organ and passed out. This applied to the urea of the urine, which was looked upon by Müller as a pure case of "excretion." The distinction thus set up has, however, not been maintained by physiologists. The term "excretion" has been, and is at the present time, applied sometimes in a vague kind of way, sometimes more definitely and specifically, to denote the process of elimination of waste products from the body. This process is frequently of the nature of secretion. Thus the elimination of urea by the kidney is referred to as a "secretion," although the product itself is an "excretion." This is due to the fact, now well established, that, although urea is present in the blood supplied to the kidneys, yet it is not simply filtered out of the blood, but is got rid of by a definite "secretory" activity of the cells of the tubules. It can be shown that the cells are capable of performing a definite chemical synthesis, and this is regarded as a sign, or one of the signs, of a "secretory" activity; so that the term "secretion" includes "excretion." When the products of metabolism are of no service in the economy, they are called "excretions."

Among the best-known of the secretions are the enzymes and analogous products (such as will be referred to later as the products of the "internal" secretions). But many skeletal substances are often included in the same category; such are the calcareous shells of the Foraminifera, the chitinous cases of insects, cell membranes, etc. Many authors would include also certain intercellular substances, such as are found in the fibrillar connective tissue, cartilage, and bone. Where, however, definite morphological structures are formed, it is well to reject the name "secretion." Thus, the products of the reproductive organs—the ova and spermatozoa—are not to be included among the secretions.<sup>1</sup>

The term "secretion" in higher animals is ordinarily meant to apply to the liquid or semiliquid products formed by the glandular organs, or to the process of manufacture and setting free of such products. The idea of secretion has, from the earliest period of physiology, been associated with what are called "glandular" organs. The term "gland" was applied in the early days of anatomy to a very varied group of structures which resembled each other only in certain general external characters.<sup>2</sup> Thus, in the same general category were included not only such typical glands as the pancreas, submaxillary glands, and kidneys, but also the liver, spleen, lymph nodules, reproductive organs, and, as they were discovered, the thyroid body, the suprarenal capsule, the thymus, and so on.

There is no need to describe a "gland" in any detail. We may now define a gland as a structure made up of one or more cells of a special epithelial character which forms a product, the secretion which is discharged upon an epithelial surface, such as the skin or a mucous membrane.

<sup>1</sup> The seminal fluid as a whole is, of course, to be looked upon as a secretion, coming partly from the testes, but chiefly from the accessory sexual glands. The secretion itself is to be regarded as a vehicle for the transportation of the spermatozoa, and possibly also for their nutrition. But whether or no we view the testis as a gland having an *external secretion*, we shall see reasons later for considering it to be a gland with an *internal secretion*.

<sup>2</sup> "Die Classe der Drüsen ist eine derjenigen welche eine Wissenschaft in ihrer ersten Jugend leichtsinnig schafft, und welche zu begrenzen und rechtfertigen ihr in Zeiten der Reife grosse Sorgen und Mühe kostet. Maas hatte anfangs nur die äussere Form in Auge und nannte jedes weiche, rundliche, gefässreiche und daher röhliche oder rothe Organ eine Drüse, und das Gewebe solcher Organe drüsig (Henle, 164).



This is the definition of an ordinary or externally secreting gland.

The simplest type of a gland consists merely of a layer of epithelial cells placed upon a basement membrane, while beneath the membrane are found blood capillaries and lymph spaces. When such a layer of epithelial cells becomes invaginated, we have a tubule or saccule possessing a lumen, and forming a simple tubular or saccular gland. Such glands may be coiled, as in the case of the sweat glands, or the secretory portions of the glands may divide, forming branched tubular glands. This branching may occur again and again, until a complicated structure is produced (compound tubular and compound saccular [or racemose] glands). In these glands the terminal portion of the tubes or "alveoli" are the secretory portions, while the tubes leading to the exterior are the "ducts." The gland cell varies in its microscopic appearance, according to its functional condition. In the submaxillary gland and in the pancreas the variations are well known and easily observed—the discharge of the zymogen granules and the growth from the base of the cell of the chromatophilous substance. Similar functional changes may be observed in the epithelium of the intestine (Asher, 10).

But it was discovered that some of these glands possessed no duct, and they were therefore called "ductless glands," or in German more usually "Blutgefäßdrüsen," or "Blutdrüsen." The latter names are, however, rapidly falling into disuse, and the terms, "ductless glands," or "glands with an internal secretion," are replacing them. The assumption was at once made that, since these structures had the characters of glands, they must "secrete." But since there was no communication with a free surface, the hypothesis soon arose that in these cases the specific secretion is passed into the blood-stream, and both the process and the product were termed "internal secretion." Thus a new conception in regard to the physiological nature of secretion sprang into existence, and the definition of a gland was extended so as to apply to any structure made up of one or more cells of a special epithelial character which form a product—the secretion—which is discharged upon a free epithelial surface, such as the skin or mucous membrane, or upon the

closed epithelial surface of the blood cavities. In some cases the material secreted by the ductless glands is supposed to be passed away not directly into the blood-stream, but indirectly by means of the lymphatics. This is usually believed to apply to the specific secretion of the thyroid gland (see, however, p. 348).

The term "internal secretion" was, so far as I can ascertain, first used in 1855 by Cl. Bernard (20), who described the glycogenic function of the liver as the "sécrétion interne," while he referred to the preparation of the bile as the "sécrétion externe."<sup>1</sup>

The glycogenic function of the liver is not at the present time usually included among the internal secretions. It is a special kind of arrangement for the storing of food material. The glycogenic function of the liver is, however, intimately related to certain internal secretions—notably those of the pancreas and the adrenal body. Moreover, there are reasons, as we shall see, for attributing to the liver other kinds of internally secreting activities.

Since the time of Cl. Bernard there has been much loose thinking and loose writing upon the whole subject of internal secretion. A great tendency has often been manifested to hasten to unwarrantable conclusions. In morphology and comparative anatomy ill-understood organs or parts of organs have sometimes been hastily and incorrectly assigned to the group of ductless glands, and in physiology many processes which were imperfectly understood have been prematurely classed among the internal secretions.

The study of the efficacy of various organs as remedial agents arose in the time of Hippocrates, and Celsus and Dioscorides recommended the use of various animal organs for the relief of those symptoms in man which were considered to be due to defective action of the same organ; hence the use of the pigeon's or wolf's liver in cases of hepatic disease, the brain of the hare for tremors, the lung

<sup>1</sup> "Chez les animaux la sécrétion glycogénique est une sécrétion interne, parce qu'elle se verse directement dans le sang. J'ai considéré le foie, tel qu'il se présente chez les animaux vertébrés élevés comme un organe sécréteur double. Il semble réunir, en effet, deux éléments sécrétoires distincts et il représente deux sécrétions: l'une externe qui coule dans l'intestin, la sécrétion biliaire; l'autre interne, qui se verse dans le sang, la sécrétion glycogénique (Cl. Bernard, *loc. cit.*).

of the fox for dyspnoea, and the use of rennet for disorders of the stomach and intestines. Pliny recommended the use of the testicles of the donkey and of the stag as aphrodisiacs; and even at the present time there remains the practice of employing castoreum for menstrual disorder.<sup>1</sup>

Much interest was aroused by the work of Brown-Séguard (39, 40, 41) in 1889 upon testicular extracts—work which demonstrated great lack of critical power in its author (*vide infra*, p. 67). Brown-Séguard put forward the theory that all tissues give off something or other to the blood which is characteristic or specific, and which is of importance to the nutrition of the body generally. This may be regarded as the real beginning of the modern doctrine of internal secretion, and represents the actual view of many modern writers, particularly in France. It will be seen that the view of internal secretion which we shall advocate is modified from this, inasmuch as secretion is only to be attributed to certain special cells, and not to all elements in the body.

Brown-Séguard's theory led to a revival of the old humoral physiology, a partial dethronement of the nervous system, and a return to the therapeutic methods called "opotherapy." The "humours" of to-day are, however, very different conceptions from those of the blood, the yellow bile, the black bile, and the phlegm of Hippocrates and Galen. The modern conceptions, indeed, could only have arisen with the growth of modern chemistry. Both physiology and pathology are becoming more and more chemical.

We shall see hereafter how very minute may be the quantities of substances which come into play in physiological actions. The phenomena of chemiotaxis, of anaphylaxis, and of the activities of ferments and toxins, all illustrate the importance of the "chemistry of imponderables." Richet (312) lays stress on the significance of individual humoral differences. "Every illness, every intoxication, has caused the formation, perhaps the destruction, of a certain substance in the blood, and has left its natural trace—a trace which is not effaced by years. Just as there is the psychological memory—facts which are present to

<sup>1</sup> These examples are quoted from Batty Shaw (342).

the consciousness—so there is a humoral memory of all preceding injections. As these injections differ in each person in intensity, quantity, and duration, it follows that each person differs from every other in the chemical properties of his blood.”<sup>1</sup>

The irritability which rules the functions of the nervous system is in itself a chemical phenomenon. Richet (*loc. cit.*) says : “ The living being is a chemical mechanism, and perhaps it is nothing more.” Such a sentence by an eminent modern physiologist illustrates the trend of present-day physiology. The attitude is reminiscent of that which became prevalent in the earlier days of Huxley’s work. The modern view of “ protoplasm ” is, however, very different from the original one, and the chemical attitude, critically restrained, will possibly do much more to explain the processes of life than all the painstaking anatomical, microscopical, and mechanical investigation of the past fifty years.

The theoretical basis for opotherapy and the practical value of this method of treatment has varied very considerably in different cases. Some flagrant examples of uncritical application of the method are the treatment of heart disease by extracts made from heart muscle, subcutaneous injections of extracts of ciliary bodies in iritis, and of synovial membranes in diseases of the joints.

Caspar Friedrich Wolff (406) long ago expressed the idea that “ each single part of the body, in respect of its nutrition, stands to the whole body in the relation of an excreting organ.” The term “ excreting ” was here used in Johannes Müller’s sense (*vide supra*, p. 2), and is practically synonymous with the modern “ secretion.” It is certain that the organs of the body produce effects upon one another in many different ways by means of the products of their metabolic activity. Conveyed in the blood-stream to different parts of the body, these products may act as agents of augmentation, or possibly inhibition, in regard to the special activities of various organs and tissues. One of the best examples of this is the so-called automatic excitation of the respiratory centre produced during asphyxia by the circulation in the blood of decomposition products

<sup>1</sup> Richet, *loc. cit.*

normally eliminated in the expired air. Again, when a large amount of protein is absorbed and digested, the products formed probably stimulate an increased metabolism in the body generally. When this occurs, urea is formed by the liver in larger amount, and stimulates the kidneys to increased activity.

In a certain sense, and in the direction just indicated, it is evident that all the tissues and organs of the body form internal secretions, for they all pass into the blood materials which have been formed as products of their metabolism. Everything which an organ or tissue absorbs from the blood and lymph it gives out to them again in some form or other, except in so far as it forms or separates a secretion which passes away by special ducts. It is obvious that in this, the broadest sense of the expression "internal secretion," nothing further is implied than that the blood which leaves by the veins coming from an organ or tissue contains different chemical substances from that which enters by the arteries. A distinction might possibly be made in some cases between *katabolic* products such as are formed by all tissues, and *synthetic* products which are only formed by some, and the term "internal secretion" might be reserved for the latter. But this distinction could not be maintained systematically, for it is quite conceivable that a definite specific and powerful internal secretion might be formed by a katabolic process. Some authors have included intracellular enzymes among the internal secretions. These are still more "internal" than the secretions usually so called, for they are not passed out of the cell in which they are produced. They differ from the exo-enzymes such as are found in the secretions by reason of the fact that they are bound up in the protoplasm of the cells, and, so long as the cells are alive, can only exert their action intracellularly. When the cells die the protoplasm breaks up, and the enzymes may pass into solution. It is supposed that these enzymes are elaborated by and used during the life of the protoplasm. It is possible that in starvation they may bring about the solution of the tissue proteins, and that the autolytic processes which take place after death are due to their activity. It has been suggested that life is nothing more than the sum-total of the

activities of the enzymes contained within the living matter.<sup>1</sup> A theory related to this has been suggested in a tentative form by Bayliss and Starling (17). In a paper on the mechanism of pancreatic secretion (a subject which will be referred to again later on, *vide infra*, p. 57), these authors tested the hypothesis that the products of metabolism of certain tissues would be found to act as vasodilators only for certain tissues in functional relation to those in which they arise, or, at all events, would act to a greater degree on these tissues than on the rest of the body in general. Results were obtained which tended to confirm their view. Vincent and Sheen (380), however, obtained different results, and suggested that the subject may be complicated by the existence not only of specific vasodilators, but also of specific vasoconstrictor substances, whose effects might be looked for on those occasions when the injection of a tissue extract produces a rise of blood-pressure.

In some modern textbooks the conception of internal secretion is extended beyond the limits which appear reasonable. Thus, Halliburton (147) states that the lymphatic glands "form an internal secretion which consists of lymph cells, and these furnish the blood with a supply of certain kinds of colourless corpuscles." It has already been mentioned (*supra*, p. 3) that definite morphological elements should be excluded from the category of the secretions. Thus, the ova and spermatozoa are not included among the external secretions, and the cells manufactured by the spleen, lymph glands, and bone-marrow must be excluded from the group of internal secretions.

The conception of internal secretion has had far-reaching effects in the realms of both physiology and pathology. Pathologists are now able to recognize the existence of new forms of stimuli which influence growth and metabolism, and this either in a positive or in a negative direction—that is to say, either in the direction of augmentation or inhibition. Thus, to mention one example, dwarfism and gigantism may be explained by reference to certain internal secretions, or, at any rate, a plausible hypothesis may be furnished by such reference. It is further to be noted that the function of each particular internally secreting gland

<sup>1</sup> For an account of these intracellular enzymes, see Vernon (372).

may be conceived as varying, or capable of varying, from the normal in the sense either of hypersecretion or hyposecretion. In the former case the amount of augmentation or inhibition may be greater than the normal ; in the latter case the amount of augmentation or inhibition will be less than the normal.

Various older pathological conceptions are now expressed in terms of the modern "internal secretion." The "consensus partium" of the early writers may be regarded as the prime function of the internal secretions. The "formative stimuli" controlling the "vegetative processes" of the body and the "sympathetic" relationships between different parts of the organism are now frequently regarded as depending upon the integrity of the ductless glands or "correlative organs."

An interesting pathological development may be mentioned in this place. Not only in various forms of physiological hypertrophy are we to suppose there is a hypersecretion of a ductless gland, but the same may happen in definite pathological overgrowth ; so that it is even believed that in tumours of the internally secreting organs—thyroid, pituitary, pancreas, adrenal—there may be actually a hypersecretion—that is to say, that the tumour cells may secrete in a specific manner.

It must be confessed that we do not know the functions of any one of the ductless glands in the same definite way in which we know the functions of, for example, the lungs or the pancreas. Owing to the lack of boundaries and the absence of precise exploration in many regions, the territory of internal secretion has been invaded by some irresponsible exploiters. The time has arrived for us to take our bearings and ascertain our precise position with regard to the subject. In doing this, every effort will be made to avoid dogmatism, even at the risk of losing, or hesitating to accept, some tempting and plausible theories.

In the following pages, after a chapter upon the definition and limitation of the term "internal secretion," it will be desirable to treat first of the general methods of investigation of the subject of internal secretion and the validity of the conclusions which may be drawn from results obtained by such methods. Afterwards the internal secretion of glands

which have also an external secretion will be dealt with. These are the liver, the pancreas, the kidney, the intestinal glands, and the gastric glands. Following these, the internal secretion of the testis and ovary (with its corpus luteum<sup>1</sup>) will be described. Then will follow in order treatment of the function of the "ductless glands"—namely, the adrenal body, consisting of "cortex" and "medulla"; the thyroid body (including the parathyroid corpuscles); the pituitary body, consisting of the "infundibular" or "nervous" portion and the "glandular" portion; and the thymus gland. Finally, there is a chapter on the pineal body.

<sup>1</sup> The corpus luteum may be looked upon as a "ductless gland," but it will obviously be convenient to treat of it along with the ovary (see p. 75).



## CHAPTER II

### DEFINITION AND LIMITATION OF THE TERM "INTERNAL SECRETION"

It is obvious at the outset that the term "internal secretion" ought to be employed in such a way that it corresponds as far as possible to the term "external secretion," or secretion by means of ducts. Secretion, as we have seen, is the preparation and setting free of certain substances, the raw material for which is supplied by the circulating blood. Such secretion is the function of certain specially differentiated cells—the secretory cells.

It has already been mentioned that several authors, relying upon the fact that the different organs and tissues of the body have different functions, and therefore pour out into the blood different metabolic products, have insisted that all these have an internal secretion, and that this secretion is in each case a specific one. But this, as pointed out by Kohn (185), is simply a misuse of the term "secretion." Just as we have certain tissues—namely muscle and nerve—highly specialized and set apart for the functions of motility and conduction of irritability, so we have certain other tissues also highly differentiated and set apart for the purposes of secretion, and it is only to these that we can with propriety ascribe the function. Such are secretory cells and their accumulations, called "glands." The secretory cells are in their origin and in their character *epithelial*. *Secretory cells are highly specialized epithelial cells.* It is not necessary to insist on this criterion in the case of externally secreting glands, because here it is generally recognized; but it is just as important in regard to internal secretion if the term is to be defined with anything approaching accuracy. The morphological sign of special differentiation in gland cells is the presence of granules which undergo

## DEFINITION OF "INTERNAL SECRETION" 13

periodical changes in number and position, according to the stage of activity of the gland. It is not, perhaps, possible to insist on the recognition of granules as definite as those in the pancreatic cells before we admit a structure into the category of internally secreting glands, but it is essential that the constituent cells should have the general character of glandular—i.e., secretory—cells. This is in some instances not altogether an easy matter to determine, and, as we shall see later on, there is still some discussion as to whether such a tissue as the *chromaphil* may reasonably be supposed to have a secretory function. That a discussion of this kind should arise in connection with a structure generally supposed to be internally secretory shows how little we know about the actual act of secretion in such a case (see p. 213 *et ff.*).

We conclude, then, that secretion (internal or external) represents a highly specialized grade of metabolic activity, and should be distinguished as rigorously from general metabolism as the contraction of muscle from general motility (Kohn).

Kohn (185) gives a very excellent illustration of the two processes, external secretion and internal secretion. The manufacture of the bile and its conveyance into the duodenum is a secretion in the ordinary sense of the word—an "external" secretion. When we obstruct the bile ducts, the secretion goes on just the same; but now the bile is conducted into the blood-stream, and we get an "internal secretion" of bile. This shows that the products of secretion can, under certain circumstances, pass into the circulation. And we can be tolerably certain that this process can in some tissues occur normally. As we have seen, it is sometimes difficult to decide whether a given tissue is glandular or not, and therefore whether we ought to ascribe to it a secretory function. Thus, Kohn admits the "cortex" only of the adrenal among the glands, while he insists that the "medulla" consists of "chromaphil cells," which are not secretory, not epithelial, and therefore cannot secrete. This point will be referred to later and more fully under the head of the adrenal body (see p. 213 *et ff.*). It may be well, however, to remark in passing that it is from the medulla, and not the cortex, that the active principle is obtained.

We are now in a position to define internal secretion. *The process consists in the preparation and setting free of certain substances of physiological utility (the raw materials for which are supplied by the circulating blood), by certain cells of a glandular type; the substances set free are not passed out on to a free surface, but into the blood-stream.*

According to this definition, the products of ordinary metabolism, and even the special products of metabolism arising in such kinds of highly specialized tissues as muscle and nerve, are excluded from the internal secretions.

We have seen that externally secreting glands sometimes manufacture and pour out substances which are waste products, and are no longer of any use in the economy. These are "excretions." It is possible that some of the substances elaborated by the internally secreting glands may also have to be placed in the category of "excretions." They would then be "internal excretions" (see p. 37).

The terms "ductless gland" and "Blutgefäßdrüse" were originally applied to a very varied group of structures, including the thyroids and parathyroids, the adrenal bodies, the thymus gland, the pituitary body, the spleen, and the lymphatic glands. But some of these—the spleen and the lymphatic glands—have not a "glandular" structure; that is to say, they do not consist of epithelial "secreting" cells, and belong to quite a different category of organs, namely, the "hæmolymph" series. The structures usually included at the present time under the title of "ductless glands" are the thyroid gland (including the parathyroids); the adrenal body, consisting of "cortex" and "medulla"; chromophil cells and bodies in different regions; the pituitary body, consisting of the "infundibular" or "nervous" and the "glandular" portion; the thymus gland; and the corpus luteum. The thymus originates as an epithelial structure, but subsequently appears to become largely converted into a lymphoid organ.<sup>1</sup> Its morphological characters are therefore unique.

It is believed that these "ductless glands" manufacture and pour, directly or indirectly, into the blood-stream some substance or substances which are of service in the economy, either by supplying a need or by destroying other substances

<sup>1</sup> See, however, discussion on p. 359.

## DEFINITION OF "INTERNAL SECRETION" 15

which are needless or positively harmful. This last function—that of "Entgiftung," an "antitoxic" function—is frequently ascribed to the thyroid, though in this, as in other cases, the two conceptions are not necessarily antagonistic. We can readily imagine that a gland may manufacture a definite internal secretion whose active principle may be competent to destroy poisonous products in the blood-stream or in some part of the body.

It is, perhaps, desirable to point out at this stage that the term "internal secretion" has been used too generally and too confidently in many cases. Our knowledge of internal secretion is not to be compared in accuracy and definiteness with our knowledge of "external" or ordinary glandular secretion. Thus, in the case of the submaxillary glands, we can observe the various conditions, loaded or unloaded, of the gland cells. We can watch the flow of the secretion, and regulate it by stimulation of nerves. We can note changes in the volume and blood-supply of the gland concomitantly with the act of secretion. Finally, we can recognize an "enzyme" in the fluid secreted, and are familiar with its chemical action on the food as a process of digestion. Very different is the case, for example, of the medulla of the adrenal body and of the chromaphil tissues generally. Here comparatively little is known of changes in the cells indicative of the act of secretion,<sup>1</sup> and the very fact that any secretion is poured into the blood-stream can only be shown, if shown at all, by laborious and indirect methods. It must be confessed, as a matter of fact, that some of our conceptions in regard to internal secretion are worthy to rank little higher than plausible hypotheses.

But a typical gland having a duct and performing "external secretion" may possess also, according to modern views, the function of "internal secretion." This applies to the liver, the pancreas, the kidney, as well as the intestinal and gastric glands. The liver has, besides the formation of the bile and the glycogenic function (which, owing to its highly special character, is usually excluded from the internal secretions), the still further duty to render innocuous the end-products of protein metabolism. One of these end-products is ammonia; this is converted in the liver into

<sup>1</sup> See, however, p. 223.

urea. So that the distinctly poisonous ammonia is transformed in the liver into the comparatively harmless urea. This is an example of what Biedl (24) calls "*negative internal secretion*." Since the process is a stage in the elimination of waste material, it might be called "*internal excretion*" (*vide supra*, p. 14).

Recently discovered and extremely interesting examples of internal secretion are furnished by the mechanisms of pancreatic and gastric secretions (*vide infra*, pp. 57 and 65).

There is considerable reason for ascribing an internally secreting function to the testis and to the ovary (*vide infra*, pp. 67 and 75). Though these are not glands in the usual acceptation of the term, yet many of their constituent cells are of the "glandular," "secretory" type.

Lane-Clayton and Starling (199, 351) have recently reported that injections of extract of foetus into a virgin rabbit causes growth of the mammary glands, while such injections into a multiparous animal causes secretion of milk. Starling suggested the name "Hormone" (from ὀρμάω = I excite or arouse) for these various substances which act as chemical messengers, and the name has in recent years become generally adopted. This subject will be referred to again and more fully in the next chapter (p. 24). In passing, it may be noted that we can scarcely regard the foetus in its entirety as a gland with an internal secretion. Many of its tissues are of the kind which is incapable, according to our definition, of furnishing an internal secretion. Foa (106) finds that injection of extract of foetal calf causes some mammary growth in rabbits. It is concluded, therefore, that the mammary hormone described by Lane-Clayton and Starling is not specific for only one kind of animal.

Heape (157) points out that it is well known that virgin animals sometimes produce milk. So that it seems clear that the beginning of the development of the gland dates from some point of time prior to or during pro-œstrum or œstrus, and occurs normally quite apart from pregnancy, and that since the full functional development of the gland may be experienced by virgin animals, this must occur without any stimulus from a foetus. Heape believes that the source of the stimulus which excites the development of the mammary glands is to be found in what he calls "gonadin,"

## DEFINITION OF "INTERNAL SECRETION" 17

secreted by the ovary at that time, if not in the "generative ferment," which, he holds, governs the activity of the generative glands.

There is now some considerable evidence that the stimulus to growth of the mammary gland arises from the corpus luteum. This will be referred to again and more fully under the head of "The Internal Secretion of the Ovary and the Corpus Luteum" (*vide infra*, Chapter IX., Sect. C., p. 75).

Arguing from these mammary gland experiments, and from those upon the mechanism of pancreatic secretion (*vide infra*, p. 57) performed in conjunction with Bayliss, Starling (352, 353, 19) has made some interesting generalizations upon this type of mechanism. He points out that in the normal life of the higher animals, looked at as a series of reactions to environmental change, the nervous system plays such a predominant part that we are in danger of overlooking more primitive means of co-ordination between different parts of the body. Starling further points out that in the lowest animals, before the appearance of a central nervous system, it is by chemical means that co-adaptation of function is achieved. As examples he mentions the movement of phagocytic cells towards an irritant, the chase for food, the escape from noxious environment, or the approach of sexual cells. In these cases the mechanism is chemiotaxis. The process of action of these stimuli must be slow, and the development of a blood-circulation is necessary in order to quicken it. But before this development occurs, the need for quick reactions has determined the setting apart of special reactive cells; we see, in fact, the rudiments of the nervous system. The whole history of the evolution of man and the higher animals centres about this nervous system.

But in some cases still, where there is no necessity for a specially rapid reaction, as, for example, in the adaptation of the activities of the digestive glands to the presence of food in the alimentary canal, one might expect to find, as Bayliss and Starling actually found, that chemical means of stimulation are employed. Among the various hormones Starling enumerates the gastric and pancreatic hormones, as well as similar bodies which determine the secretory

activity both of the liver and the intestinal glands, adrenin, thyriodin, and the substance secreted by the fœtus during pregnancy. He prophesies that with increasing knowledge the list of these messenger substances will be largely extended, he points out that they are comparable in many respects to the alkaloids, and he intimates that the practice of drugging would therefore seem to be not an unnatural device of man, but the normal method by which a number of the ordinary physiological processes of the organism are carried out.

How far this attitude may be justified by future discoveries must at present remain doubtful, but it certainly represents the view of a large number of modern workers upon the subject of internal secretion. The nervous system is no longer the only controlling influence to be reckoned with in explaining the bodily functions, and especially is this the case with the co-ordination and interactions of many of the chief functions of the body. It is even possible that the nervous system itself may be controlled by chemical stimuli.

A. S. and Helen G. Grünbaum (131) have performed some experiments to test the hormone theory of the causation of new growths. The work of Starling and Claypon upon the internal secretion of the fœtus in relation to the mammary gland suggested that perversion of internal secretion might have some relation to the formation of new growths. Such a hypothesis presupposes the existence within the organism of separate substances which stimulate the normal growth and repair of the several organs and tissues, and that each substance is secreted either by its own special organ, or by another organ or tissue. Under the former supposition, so the authors imagine, malignant growth of such tissue would be very unlikely. Under the latter the result might be brought about either by hypersecretion of the substance or by insufficient absorption thereof, whereby in either case the still absorbing tissues would receive an excess. Given an excess of hormone in the organism, together with a lesion or irritation of the tissue complementary to the hormone, unlimited growth might result. It is further conceivable that a real hypersecretion acting on otherwise normal tissue might lead to the formation of a

## DEFINITION OF "INTERNAL SECRETION" 19

quickly increasing growth, while the relative hypersecretion resulting from diminished absorption from an atrophied senile membrane might account for slow-growing tumours.

The authors inoculated previously refractory rats with pieces of glandular organs from known susceptible animals, along with sarcoma. The results in two experiments seemed to show that parotid gland is able to assist sarcoma growth in rats otherwise insusceptible. They further excised the parotid along with inoculation with sarcoma to see if the growth of the tumour was inhibited. The results were not very definite.

Ehrlich (87A) thinks there may be substances circulating in the organism which may stimulate the body cells to resist the athreptic influence of cancer cells. Askanazy (10A) believes that certain hyperplasias in the genital organs subsequently to the formation of tumours in the ovary, testis, or pineal body, may be due to the influence of embryonal tissue formed by the tumour. [See, however, Frank and Unger (113A)].

The object of the present chapter has been to define as accurately as possible what we mean by internal secretion. The point of greatest importance is to limit our conception of internal secretion so as to include only those processes which are comparable to ordinary or external secretion. We must only allow of the hypothesis of internal secretion in cells which are of a glandular type, and we must diligently search for all signs of cellular activity indicative of secretion. We must further strive to study the process of secretion itself, to discover the products of secretion, to trace them out into the blood-stream, to follow them to their place of activity, and to find their ultimate destination.

In the next chapter we shall study some of the methods of such investigations.



## CHAPTER III

### GENERAL METHODS OF INVESTIGATION AND THE VALUE OF THE RESULTS WHICH MAY BE OBTAINED BY SUCH METHODS

IN the investigation of a subject of such wide physiological import as internal secretion, it is natural that all methods employed in general physiological research should be utilized as occasion demands. The usual methods of experimental physiology, recording devices, and all the appurtenances belonging to the graphic method, are in regular requisition. Physiological chemistry is no longer a mere handmaiden, but is rapidly becoming mistress of the situation. No attempt will be made to pass in review all these details of scientific biological method. A few of the more important methods which have been of especial service in the development of the subject of internal secretion will be briefly referred to, and an opportunity will at the same time be seized to deal with a few side issues which could not conveniently be treated in any other chapter.

The subject of internal secretion is, of course, a physiological one, but we shall again and again have occasion to make reference to *pathological* methods and pathological facts. This is perhaps more emphatically the case than in any other chapter in physiology, because such a large proportion of our knowledge of internal secretion is derived from the realm of pathology, not only from *human pathology*, but also from *experimental pathology*, the result of experiments upon animals.

The fact discovered by Addison in 1855 that the symptoms of what is now known as Addison's disease are due to a lesion of the adrenal bodies is still one of the most important pieces of information we possess about these struc-

tures. The association of defective thyroid development or atrophy with cretinoid and myxœdematous conditions is still the sheet anchor of our knowledge of the thyroid apparatus. The same may be said of the pituitary body and acromegaly, and doubtful as may be the connection between enlarged thymus and sudden death in infants, yet this is almost the only allegation which points to the organ having any definite function.

*Experimental pathology* in the form of *extirpation experiments* has been largely employed in the attempt to elucidate the functions of the glands with an internal secretion. The method has undoubtedly brought to light many important new facts. It has revealed, for example, the fact that certain of these glands, such as the adrenal and the pituitary, are essential for life, and that removal of the thyroid apparatus entails in most animals very serious results. It has taught us, further, that extirpation of the thymus is without obvious effects. But the results obtained by different observers have often been very contradictory, and the method of complete extirpation has several drawbacks. In the first place the technical difficulties are always very considerable, and are often wellnigh insurmountable. This applies especially to the pituitary body, though modern surgical skill seems at last to have triumphed (see p. 382). It is very frequently impossible to remove just the organ one wishes to remove without doing considerable damage to other tissues. Thus the extirpation of the adrenal bodies and the thyroids must always involve considerable injury to nervous structures and bloodvessels. This consideration must largely account for the contradictory results obtained by different observers. The difficulty of removing the parathyroids without doing considerable injury to the thyroids can scarcely be overcome, and the successful removal of the pituitary cannot have been performed by more than a very few observers.

Again, we must remember that complete removal of an organ, even if successful from a surgical standpoint, is, owing to its suddenness, an event which can never happen in nature, and can never happen in pathology, and we must be cautious in interpreting the results. The method, however, under modern surgical conditions, is capable of fruitful

results, for animals do not appear to suffer to any considerable degree from surgical shock.

Extirpation experiments performed in a series of steps at successive operations are more valuable than when the whole of an organ (or both organs in the case of bilateral structures) is removed at once. Better still and more fruitful of results are operations in which the organs are crushed, damaged, or infected artificially with the germs of disease, or inoculated with toxins, or partially destroyed by chemical poisons, or in which the blood-supply is interfered with to a more or less complete degree.

Further, extirpation experiments, as usually performed, are only likely to give us useful information in cases where the organ or tissue extirpated normally provides an internal secretion which is needful for the body as a whole. If we remove the submaxillary glands, for example, we find that the animal is apparently unaffected, and the same applies to the mammary and gastric glands. But we are not justified in concluding from these experiments that the glands in question have no internal secretion, but merely that if there be such a secretion, it cannot be regarded as essential to the body as a whole. As a matter of fact, it is now believed that the gastric mucous membrane secretes a specific hormone (*vide infra*, p. 65), and the same has recently been thought to be the case with the salivary glands. Hemmeter (163) states that the total extirpation of the salivary glands in the dog brings about a marked diminution of the secretion of gastric juice, which can be increased again by giving extracts of the glands intravenously or intraperitoneally. The salivary glands, therefore, in his opinion, furnish an internal secretion which stimulates gastric secretion.

Proceedings of a reverse character, such as *grafting*, *feeding*, and *subcutaneous and intravenous injections*, have also been extensively employed in the search for the functions of the ductless and other glands supposed to possess an internal secretion. Experiments in grafting have been chiefly carried out in connection with the thyroid and parathyroid glands, and the reproductive organs. Some work in the same direction has also been done with the adrenals. The object of these experiments has been to replace the extirpated tissue by freshly implanted tissue of

the same kind, either in the original situation or in some other part of the body. The earlier attempts were not very successful, and the effects were of a temporary character. The graft became absorbed, and so the final result was no more than that of the administration of a certain dose of the substance of the gland. Some recent experiments, however, have been more successful, and have yielded interesting and important results. An account of these grafting experiments will be given in their appropriate place under the heads of Thyroid, Adrenal, and Reproductive Organs.

*Feeding* with fresh tissues, or with tissue extracts prepared in various ways, has been very extensively employed. The therapeutic method called "opotherapy" is based upon the principle that the active substance, the "hormone," or the "internal secretion," is absorbed unaltered into the circulation. This is apparently a matter for discussion in some cases, as, for example, in the case of the adrenals (*vide infra*, p. 210). On the other hand, feeding with thyroid glands or thyroid extracts (or even with the so-called active principle, iodothylin or thyroiodin) has proved a most valuable mode of treatment in cases of cretinism and of myxœdema, and has, besides, been used by physiologists for experimental purposes. But our knowledge of the functions and internal secretions of most of the glands, and especially of their true and intimate relationships to morbid processes and pathological conditions, is still so limited and inexact that it can hardly be expected to furnish guidance in treatment. More especially is this true in regard to the pituitary body, the thymus, and even the pancreas. The tissues which have been considered from the standpoint of *opotherapy* or *organotherapy* are, in addition to the thyroid apparatus and the adrenals, the glands of the alimentary tract, the ovary, the testis, the pituitary body, the thymus, the spleen, the bone-marrow, the lymphatic glands, muscle, nerve, and the placenta.<sup>1</sup>

*Subcutaneous injections* of extracts (either fresh or after various modes of extraction and preparation) was the method which first aroused modern interest in the subject of internal secretion. The work of Brown-Séquard (39, 40, 41), in 1889, upon testicular extracts was, perhaps, of doubt-

<sup>1</sup> For an account of the work see Shaw (342), Easterbrook (82, 83, 84).

ful value in itself, but it served to stimulate research in various directions, and led directly or indirectly to very valuable results. Subcutaneous or *intra-peritoneal* injection of all other tissues and glands has since been carried out, and the results will be referred to in their proper place. By far the most striking are those obtained by the injection of extracts of the adrenal bodies (*vide infra*, p. 154).

Hildebrandt (171) has suggested that during pregnancy an impulse is exerted by the developing ovum on the mammary glands which acts as a stimulus to growth, and at the same time protects the cells of the gland from those autolytic disintegrative processes which occur to a large extent in the secretory gland. The matter was put to the test by Lane-Clayton and Starling (17). These observers made extracts of fœtuses by rubbing up with sand, extracting with normal saline, centrifuging and filtering through a Berkefeld. The animals used for experiment were then injected subcutaneously with the extracts. In virgin rabbits a growth of mammary gland was produced, and in multiparous animals a secretion of milk. The authors believe that their experiments show that the growth of the mammary glands during pregnancy is due to the action of a specific chemical stimulus ("hormone") produced in the fertilized ovum. The amount of this substance increases with the growth of the fœtus, and is therefore largest during the latter half of pregnancy. As we have seen (*supra*, p. 16), Foà (106) finds that the mammary hormone is not specific, and Miss Lane-Clayton and Professor Starling do not claim that their conclusions are firmly established. The subject is a very interesting one, and there is obviously need for further experiments in this direction.

*Intravenous injection* does not appear to have been much used in the study of internal secretions until the publication by Oliver and Schäfer (264) of the extraordinary effects upon the heart and circulation produced by the injection of adrenal extracts, or in more modern phraseology, by extracts made from the chromaphil tissue included in the adrenal (see p. 164 and Figs. 19, 37, 40, 42, 43, 44). Since that time, however, the method has been used perhaps to a greater extent than any other. Numerous observers have tested the effects of every imaginable organ and tissue in

the hope of finding some remarkable substance in the extracts comparable in its effects with adrenin from chromaphil tissues. Briefly, the results have been as follows. One other tissue besides the chromaphil—namely, the nervous portion of the pituitary—has been found to contain a pressor substance. All other organs and tissues, but especially nervous tissues, contain a depressor substance, or depressor substances (see Figs. 1-9, 90, 91).

The subject of intravenous injection of tissue extracts has played such a large part in connection with internal secretion that it must be dealt with in some detail. Considerable *naïveté* has been displayed by many observers, both as to details of method and as to the interpretation of the results obtained. Thus, for example, it has too often been assumed that a slight rise or fall of the blood-pressure obtained after injection of a fluid into the circulation is in reality due to some specific action of the extract, and not due, as it very likely is, to its effects *qua* fluid, or to its temperature, or to the rate of injection, or to some other adventitious circumstance. Again, it has in many cases been rashly concluded that because an extract of a certain tissue or organ produces a certain effect, for example, on the blood-pressure, that this is evidence of an internal secretion on the part of the tissue or organ in question. This unjustifiable attitude is being continually maintained. Thus, Livon (216, 217) divides the glands of the body into two groups, "hypertensive" and "hypotensive," according as their extracts when injected into the circulation of an animal cause a rise or a fall of the blood-pressure. The adrenals, the pituitary, the spleen, the kidney,<sup>1</sup> and the parotid, are placed in the former group; the liver, lung, pancreas, thymus, ovary, and testis in the latter.

As we have seen, the remarkable discovery of Oliver and Schäfer (264) stimulated numerous observations upon the special physiological effects of extracts made from different organs and tissues. Oliver and Schäfer noted, in addition to the effects of adrenal extracts, that pituitary extracts also produce a rise of blood-pressure. And we may state at the present time, with some degree of certainty, that these are

<sup>1</sup> It is doubtful in any case whether the spleen and kidney would be included in the pressor group. (In regard to the kidney, see pp. 33 and 51.)

the only two tissues in the body an extract of which produces *pressor* effects.<sup>1</sup>

Professor Schäfer also, working in conjunction with the present writer (327, 328), found that a *depressor* substance is also present in pituitary extracts, and noted "a certain similarity of physiological action between nervous matter and the infundibular part of the pituitary." A striking result in some of our experiments was the causation of very extensive irregularities in the blood-pressure curve after



FIG. 1.—Dog. A.C.E., morphia, curare, artificial respiration. Loop of intestine in air plethysmograph. Injection of 1.5 c.c. decoction cat's brain (Osborne and Vincent).

injection of brain extracts. Schäfer and Moore (326) had previously noted a lowering of blood-pressure on injection of brain extracts, but they did not lay any stress on the observation. Professor Osborne and the author (Osborne and Vincent, 269, 270, 271) worked out fully the effects of nervous-tissue extracts, and found that extracts made from all parts of the nervous system produce a marked temporary fall of arterial blood-pressure, which can be obtained after

section of both vagi and after administration of sufficient atropin to abolish vagus action (see Figs. 1 to 5). We came to the conclusion (contrary to that of Mott and Halliburton) that, although choline was present in small amounts in the extracts, the depressor effect was not due to the presence of that substance. The reason for this view was that, whereas after the administration of atropin to an animal, choline always produces a rise of blood-pressure, these extracts, on the contrary, always produced a fall.

<sup>1</sup> See, however, discussions in regard to kidney extracts (pp. 33 and 51).

Figs. 1 and 2 show the effects of extracts of brain and spinal cord upon the blood-pressure, the volume of the intestinal wall, the volume of the hind-limb, and upon the contraction of the auricle and the ventricle of the heart.

Figs. 3, 4, and 5 show the difference in action between nervous-tissue extracts and choline in an atropinized animal.

Nearly a year later Halliburton<sup>1</sup> (144) published a paper dealing with the same subject. His conclusions were the same as those of Osborne and Vincent, except that he considered that the effects of nervous-tissue extracts could be explained on the hypothesis that choline was the principal active agent in the solution used. He arrived at this conclusion because in his experiments, after the administration of atropin, neither choline nor nervous-tissue extracts produced a fall of blood-pressure. The present writer and Mr. Sheen (379, 380) showed conclusively from their experiments that choline

could not be the active substance in nervous-tissue extracts.<sup>2</sup> These observers, however, found that a de-

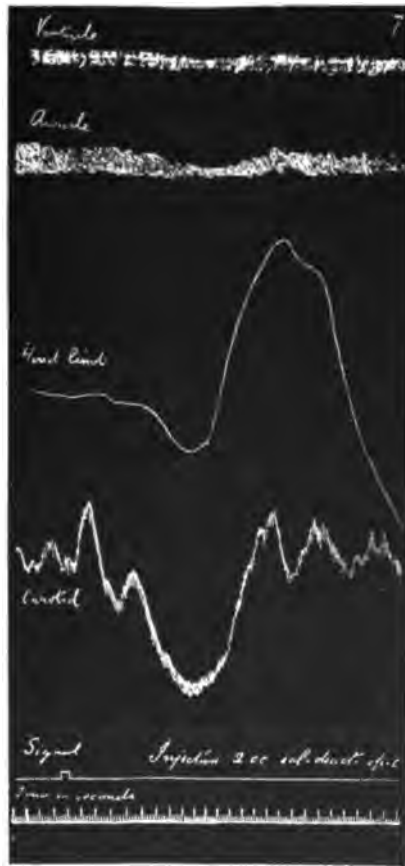


FIG. 2.—Dog. A.C.E., morphia, curare, artificial respiration. Hind-limb plethysmograph. Hooks in auricle and ventricle. Injection of 2 c.c. saline decoction spinal cord (Osborne and Vincent).

<sup>1</sup> Preliminary communications on the same subject had, however, appeared by Osborne and Vincent (269), and by Halliburton (143), in February, 1899.

<sup>2</sup> See also Osborne and Vincent (270). Other papers bearing on this question are Cleghorn (59) and Hunt (173).



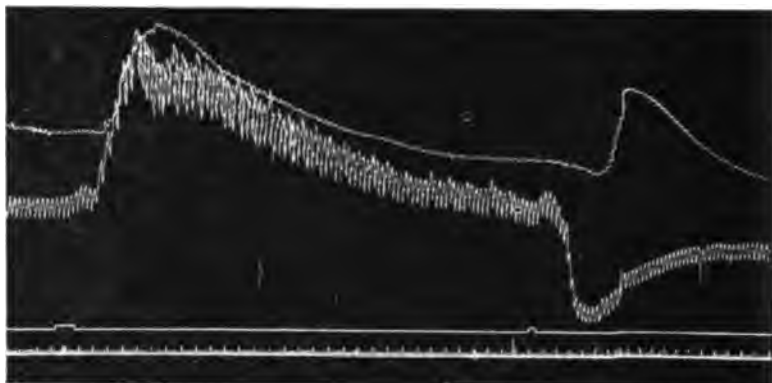


FIG. 3.—Dog. A.C.E., morphia, curare, artificial respiration, atropin. The first injection = choline. The second = saline decoction of brain. (Osborne and Vincent).



FIG. 4.—Cat. A.C.E., morphia, atropin. First injection = 1 c.c. of 0.2 per cent. choline. The second = 1 c.c. brain decoction (Osborne and Vincent).

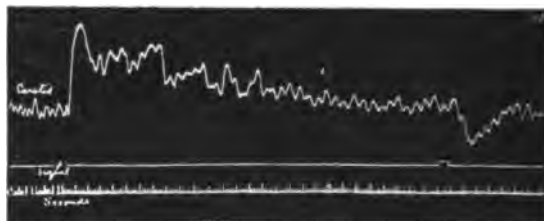


FIG. 5.—Rabbit. A.C.E., morphia, atropin. First injection = choline. The second = brain decoction (Osborne and Vincent).

pressor substance can be extracted, not only from nervous tissues, but also from all kinds of muscular tissue, kidney, liver, spleen, testis, pancreas, ovary, and lung. They note, also, that other observers have extracted a depressor substance from thyroid, thymus, adrenal, and pituitary body.<sup>1</sup>

Figs. 6, 7, and 8 show the effect of injection of extracts of muscle. Fig. 9 shows the effect of brain extract for the purpose of comparison.

By this time it had become tolerably clear to the present writer that all animal tissues impart to watery or saline

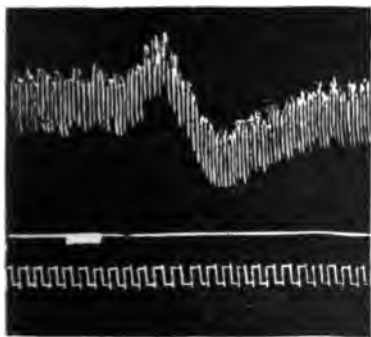


FIG. 6. — Dog. A.C.E., morphia. Injection of 5 c.c. "protein" extract of striped muscle (Vincent and Sheen).



FIG. 7. — Dog. A.C.E., morphia curare, artificial respiration. Upper curve = limb; middle curve = intestine; lower curve = carotid blood-pressure. Injection of an ether extract of striped muscle (Vincent and Sheen).

extracts a substance or substances which, when injected into the circulation of a living animal, affect the arterial blood-pressure. The effect produced by these substances is depressor, with the exception of the medulla of the adrenal ["paraganglion suprarenale" (Kohn)], other groups of chromaphil cells, and the infundibular portion of the pituitary body. It had also been rendered probable that these depressor effects of an extract are not to be regarded as an indication of an internal secretion on the part of the

<sup>1</sup> Schäfer (324); Svehla (361, 362); Moore and Purinton (255); Schäfer and Vincent (328).

tissues in question.<sup>1</sup> This seems now to be generally recognized, and the view is adopted in the majority of textbooks.

It is naturally of some interest and importance to ascertain as far as possible how far the active substances are identical in different tissues.

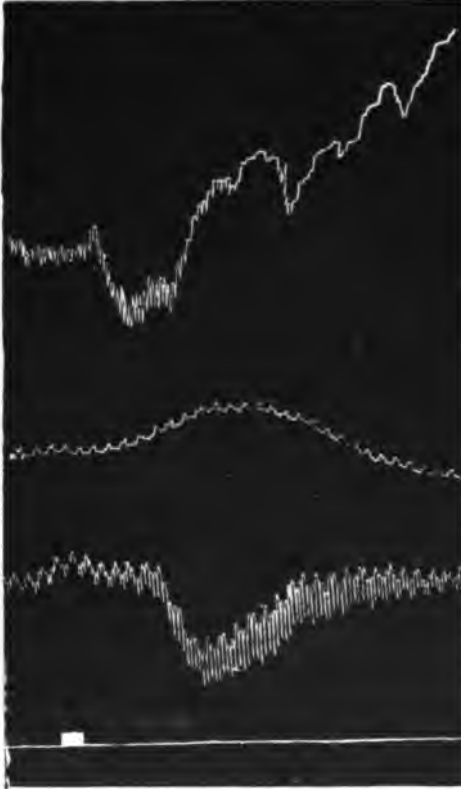


FIG. 8.—Dog. A.C.E., morphia, curare, artificial respiration. Upper curve = intestine; middle curve = limb; lower curve = carotid blood-pressure. Injection of 5 c.c. saline decoction striped muscle of rabbit (Vincent and Sheen).

The present writer, working in conjunction with Dr. Cramer (375, 376), found that there are two groups of substances in watery extracts of nervous tissues, which, when injected into the veins of an animal, lower the blood-pressure. Both of these groups are soluble in water. One group is easily soluble in absolute alcohol, and the other scarcely soluble in this fluid. The alcoholic solution contains two depressor substances; one of them has its effect abolished by atropin, the other has not. The latter is the more powerful, but rather the less soluble in alcohol.

The alcoholic solution gives an abundant precipitate with platinum chloride. Only a small part of this is readily soluble in water, and on purifying gives octahedra

<sup>1</sup> Svehla (361) states that the thymus of the human embryo does not contain the depressor substance, and considers that the presence of a depressor material in the thymus of a child at a later date is evidence of an "internal secretion." But he appears to have been unaware that extracts of nervous, glandular, muscular, and other tissues, all produce a fall of the blood-pressure.

and prismatic crystals. The greater part of the precipitate consists of the platinum chlorides of potassium and ammonium. The octahedra are the ammonium salt. Since the prisms have a percentage of 32.8—*i.e.*, 1.2 per cent. higher than would correspond to the platinum salt of choline—and since the free base has a physiological action slightly different from that of choline, it would follow that

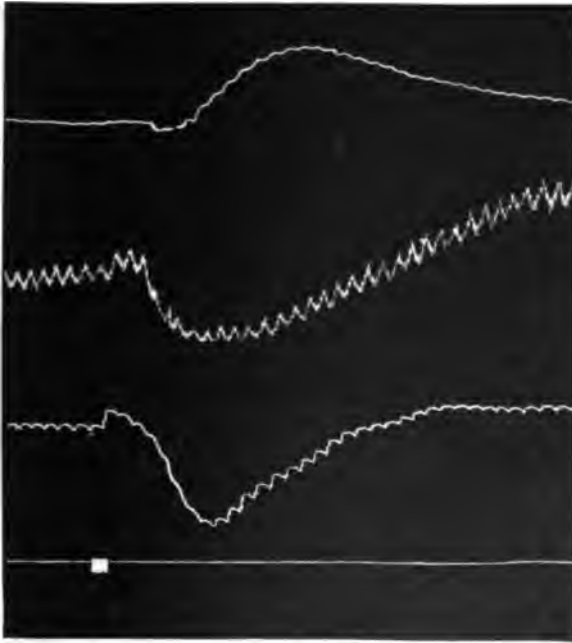


FIG. 9.—Dog. A.C.E., morphia, curare, artificial respiration. Upper curve = limb volume; middle curve = intestine; lower curve = carotid blood pressure. Effect of injection of 5 c.c. alcoholic extract of rabbit's brain (Vincent and Sheen).

the base is not choline, but a choline-like body, perhaps a di-choline anhydride.

Apart from this choline-like body, we did not find any choline as such in brain extracts, and we fully confirmed the view of Osborne and Vincent, and Vincent and Sheen, that the depressor effects of nervous-tissue extracts are not due to choline. We stated [in opposition to Halliburton (144-149)] that the chemical and physiological tests recommended for choline in pathological blood cannot be relied

upon; indeed, normal blood gives both the octahedral crystals and the depressor effect on the blood-pressure. This result has been recently confirmed by Webster (390).

Gautrelet (117, 118) adopts the naïve attitude that "les différentes glandes hypotensives" [cf. Livon, *supra* (216, 217)] have a common active principle, and that this is choline. Now, it has been abundantly proved that the chief active principle in brain extracts is not—indeed, cannot be—choline, for it possesses different physiological properties (Osborne and Vincent, Vincent and Cramer, Vincent and Sheen, *loc. cit.*). It has further been shown (Vincent and Cramer, *loc. cit.*) that there are powerful active principles insoluble in absolute alcohol, and others soluble in both ether and alcohol. Gautrelet says: "Le rôle de la choline nous semble donc capital dans l'organisme; elle répond à la définition de l'hormone telle que la conçoivent Bayliss et Starling nous considérons volontiers le système des glandes à choline (cholinogène) comme antagoniste du système des glandes adrénaline (chromaffine): de la mise en jeu des deux systèmes dépend la régulation de la pression sanguine. La présence commune de la choline dans un certain nombre de glandes explique aussi les synergies qu'ont observés les auteurs entre elles."

Even if the action of tissue extracts were in reality due to choline, there would be no grounds for such an assumption as is here put forward. The theory that the normal blood-pressure is maintained by a series of antagonistic chemical messages arriving from the different glands and tissues of the body has been put forward previously in different forms, but there is no experimental evidence to support it. The question as to what part in the maintaining of the normal blood-pressure is sustained by the chromophil tissues and by the nervous (posterior) lobe of the pituitary will be discussed in detail at a later stage.

Popielski (301) has misunderstood the views of Osborne and Vincent, and has named their depressor substance "vasodilatine" (see Dale, *Journ. Physiol.*, xli. and xliii.).

Schwartz and Lederer (337), who worked with extracts of thymus and lymph glands, arrived at the same conclusions as Vincent and Cramer, but do not mention their paper. They state that before them nobody had attempted

to identify chemically the depressor substances! So also Modrakowski (253), and v. Fürth and Schwarz (116), make no mention of the work of Osborne and Vincent.

In a paper by the present writer on the physiological effects of extracts of thymus (374), it is shown that this organ, like other animal tissues, yields a depressor substance soluble in water, alcohol, and ether. The substance cannot be choline, and this is clear for both chemical and physiological reasons. What is the nature of this substance is still unknown.

Vincent and Sheen (379, 380) believed that many tissues and organs yield pressor substances as well as depressor. Ne obtained the pressor effects most readily from simple unboiled ("protein") extracts. These results were, however, not comparable in degree with those obtained from chromophil and pituitary extracts, and, moreover, were not very constant. Fig. 6 shows the kind of effect which was obtained. Tigerstedt and Bergman (365) state that a substance may be extracted from the kidneys of rabbits which, when injected into the bloodvessels of a living rabbit, causes a rise of the blood-pressure. They get the same effect from the blood of the renal vein. They conclude, therefore, that a substance for which they suggest the name "renin" is normally secreted by the kidney into the renal blood, and that this substance causes a vasoconstriction.<sup>1</sup> This pressor substance is destroyed by boiling. The presence of a pressor substance in kidney extracts was noted also by Vincent and Sheen (*loc. cit.*), and by Batty Shaw (343). The latter observer believes there may be some relation between these effects and the "auto-intoxication" in kidney disease which gives rise to vascular hypertension. This question as to the presence of a pressor substance in kidney extracts is very interesting, and the present writer is performing more experiments upon the subject at the present time. Popielski (300) has quite recently described what he calls "eine neue blutdrucksteigende Substanz der Organismus"; but it is probable that he has observed nothing more than was described by Vincent and Sheen, Tigerstedt and Bergman, and Batty Shaw.

<sup>1</sup> See, however, Lewandowsky (211).

Abelous and Bardier (1, 2) find in normal urine a substance which raises the blood-pressure. This substance they call "uro-hypertensine," but it is satisfactory that so far there has been no suggestion that this is any kind of "hormone" or evidence of an "internal secretion."

But, of course, the effects upon the blood-pressure are not the only actions of tissue extracts which have been studied. The influences which such extracts exert upon the heart are studied by recording directly the heart movements either in the body or isolated in the lower vertebrata, and in mammals, and various forms of tonometers and plethysmographs have been employed for registering changes in the volume of the heart. The muscle-nerve preparation may be used to demonstrate the action of the extracts upon muscle and upon nerve. The volume of organs, the rate of flow of secretions, and the movements of muscular tissues, are also observed. In fact, all the modern methods of observing and recording changes in physiological conditions are constantly employed for the study of the action of tissue extracts.

An interesting method of studying the action of animal extracts on the peripheral vessels was employed by Oliver (265). The vessels of the frog's mesentery were observed before and after the application of a drop of normal saline (as a control) and of normal saline containing 1 per cent. of the organ dried at 38° C.—the simple saline and the saline extract being exactly of the same temperature (16° C.). Throughout each observation the micrometer scale was kept *in situ* over exactly the same portion of an artery and its companion vein; and when any change of calibre was observed to follow the application of the saline extract its duration and degree were noted until the calibre was restored, and it was accepted as the effect of the extract when it exceeded the normal variations and when it was practically immediate, was invariable, and when it lasted a certain uniform time, and was succeeded by restoration of the calibre. There was not much effect except in the case of adrenal extracts. This constricting effect of adrenal extract on the peripheral vessels may likewise be observed by the unaided eye by setting up inflammation of the conjunctiva in a rabbit (as by touching the eyeball with a

glass rod dipped in acetic acid) and then dropping the extract on the injected surface, when the redness quickly vanishes, and remains absent for about half an hour.

But even if, on injection of an extract of an organ, we get several different effects on the organism, it is obvious that we have no right to assume on these grounds alone that the organ yields an "internal secretion." This may be suspected when the extract yields a substance having very special physiological actions, but can be definitely stated only when the organ consists of glandular "secreting" cells which show histological signs of activity (granules, etc.), and when the blood which leaves the organs by its veins can be found to contain the same active principle as the organ itself. To make the evidence for internal secretion complete, it ought to be possible to recognize in the symptoms produced by extirpation of the organ the direct and reasonable effects of absence of the active principle, the internal secretion, and to remove these symptoms by replacing the organ in some other part of the body or by administering the active principle in some form or other.

The employment of *cytotoxic sera* as a means of investigating the tissues concerned in internal secretion has so far not yielded any results of importance. The antibodies obtained are not specific for any particular organ or tissue.

It seems to the present writer that one of the methods which will yield the most valuable results in the near future is the oldest of all—namely, careful study of clinical conditions and a patient investigation of pathological anatomical findings. Now that the microscopical structure and the comparative anatomy has been worked out with some completeness, and the results of extirpation experiments and the action of organ extracts fairly well known, pathologists may return to the problems with a better foundation of knowledge and fresh hopes for future discovery.



## CHAPTER IV

### THE NATURE, MODE OF ACTION, AND ORIGIN OF HORMONES

HORMONES may conceivably be of two kinds—namely, *augmentary* and *inhibitory*—analogous in their action to the two well-known kinds of nerve fibres. But it would seem probable that the inhibitory is in many cases the only active influence exerted. This may be regarded as a putting on of the brake, while the augmentary influence is simply a case of removing the brake. In other words, the organs have a superabundance of stored energy, and are constantly tending to over-activity. The normal degree of activity is determined by *inhibitory* influences. These influences may be nervous, or, as we have seen, they may be chemical.

But there seem to be some definite examples of *augmentary hormones*, as, for example, secretin and adrenin. The two groups are sometimes called “assimilation” and “dissimilation” hormones.

Nothing definite can be stated about the origin of hormones in general. In the case of some of the individual hormones, the matter may be discussed in its proper place.

The hormones which have so far been described are secretin, the gastric hormone, the hormones of the liver, pancreas, kidney, testis, ovary, and corpus luteum, as well as adrenin and the active substances of the thyroid apparatus and the pituitary body.<sup>1</sup>

<sup>1</sup> Zuelzer, Dorhn, and Marzer (several papers since 1908) have described the property which extracts of certain tissues (gastric and duodenal mucous membrane and spleen) have of exciting intestinal peristalsis. They refer to a “peristaltic hormone.” See also Enriquez et Hallion (*C. R. Soc. de Biol.*, t. lxxi., 1911).

A substance called “hormonal,” said to contain a solution of the hormone which causes normal peristalsis, has been recently put upon the market.

## CHAPTER V

### THE INTERNAL SECRETION OF THE LIVER

As stated in a preliminary manner above, the liver has, in addition to the formation of the bile, several important metabolic duties. The chief of these, the glycogenic function, has already been alluded to, and although to it was first applied the name "internal secretion," we shall not treat of the subject any further, for the reasons that the process is a highly special one, and that it would occupy too much space to treat of the enormous literature of the subject.

A word or two, however, ought to be said about the duty of the liver in rendering innocuous the end-products of protein metabolism. There are many facts which point to the significance of the liver in the production of urea. In the dog, when the arterial blood-supply is completely cut off from the organ, the ratio of the urea to the total nitrogen of the urine falls considerably [Doyon and Dufourt (79)]. The liver can manufacture urea not only out of  $\text{NH}_3$ , but also from other nitrogenous bodies [Salaskin (318, 319)]. So far as the production of urea from ammonia compounds is concerned, the process involves an antitoxic action, the distinctly poisonous ammonia being transformed into the comparatively harmless urea. This is what Biedl (24) calls a "negative internal secretion," and what has already been referred to as "internal excretion"<sup>1</sup> (pp. 14, 16).

There are, however, probably several sources of urea in the body, and several distinct places of origin.<sup>2</sup>

<sup>1</sup> Other papers bearing on this subject are: Salaskin (318); Allyre, Chasserant et Ricket (7); Schwarz (336); Halsey (153); Schöndorf (331); Jouve (175); Gottlieb u. Schroeder (120); Salaskin u. Zaleski (320); Gulevitch u. Jochelson (136); Biedl u. Winterberg (26).

<sup>2</sup> Gulevitch (135).

The liver is stated to be antitoxic also for other poisons, such as strychnine and nicotine, but not for atropin and curare [Rothberger (313) ; Rothberger and Winterberg (315)]. According to Charrin (55) the protective action of the liver in certain intoxications is probably due to its action on the coagulability of the blood.

According to some authors extracts of the liver are toxic. Mairet and Vires (233) find that injection of a watery extract of rabbit's liver into the veins of another rabbit causes various severe affections of the respiration, heart's action, and the nervous system, and a dose of 60 grammes per kilogramme of body weight is fatal. The efficiency disappears on beating the extract. Of course, these are enormous doses. It is probable that in corresponding doses other animal extracts prepared in the same way would be equally injurious.

## CHAPTER VI

### THE INTERNAL SECRETION OF THE PANCREAS

THE most usually quoted example of a gland which has both an internal and an external secretion is the pancreas. A relation between diseases of the pancreas and diabetes had long been suspected,<sup>1</sup> but Minkowski and Mehring (249, 251) first definitely showed that complete removal of the pancreas in the dog, cat, and pig is followed by diabetes having the usual symptoms of that disease in man.<sup>2</sup> That this is caused by the absence of an internal secretion is proved by the facts that it does not occur if the gland be left *in situ* and the duct tied, nor does it occur if a portion of the pancreas be grafted in some situation remote from its normal position (*e.g.*, underneath the skin or in the peritoneum). How the internal secretion of the pancreas normally prevents glycosuria is not clear. We can only say that it exerts some influence upon the carbohydrate metabolism, either by favouring the formation of glycogen in the liver from the glucose taken to it by the portal vein, or by furthering the oxidation of glucose in the tissues generally.<sup>3</sup>

Pflüger (283, 284, 286, 287) has recently confirmed the observation of Marcuse (237) that extirpation of the pancreas in the frog produces the same symptoms as in mammals. He also makes the further statement that extirpation of the duodenum or separation of the duodenum from the

<sup>1</sup> Lanceraux (196, 197), Baumel (12, 13).

<sup>2</sup> The experiments have been repeated by Dominicis (78), Hédou, Thiroloix, Gley, and Lépine (numerous papers in French journals up to 1898), and the work extended in the following recent communications: Kausch (178), Hugonnet and Doyon (172), Colosanti and Bonani (61), Tuckett (368), Gley (126), Ellinger and Seelig (89), Camus and Gley (48), C. Wegole (391), Allan (5), Pearce (276), Heinsheimer (161).

<sup>3</sup> Schäfer (325): see also Mohr (254), Pflüger (280-285), Minkowski (248), Schulz u. Zuegler (334), Witzel (405), Allard (6).

pancreas—the blood-supply of the gland being left intact—has the same effect. Pflüger criticizes the ordinary internal secretion theory of the pancreas, and substitutes for it a theory according to which there exist nerve centres, stimulation of which determine the production of sugar, and other centres of an antagonistic nature determining an internal secretion of the pancreas, which internal secretion hinders the production of sugar. In removing the pancreas these centres are necessarily damaged, and the same happens in extirpation of the duodenum or separation of the duodenum from the pancreas.

These views of Pflüger are opposed by Ehrmann (88), Lauwens (201), Rosenberg (314), and Minkowski (250) so far as mammals are concerned.

Herlitzka (168, 169), working with frogs, agrees that the ganglia in the wall of the duodenum are necessary for the normal internal secretion of the pancreas, and agrees with the doctrine of Pflüger that the correlation between duodenum and pancreas is due to the action of these ganglia.

Vahlen (370) points out that it is usually believed that there is in the pancreas a material which promotes the destruction of sugar in the organism, and that this unknown substance splits up the sugar in some way and thereby makes oxidation easier. The author referred to has tried to isolate such a substance, with entirely negative results, but he thinks he has obtained a constituent of the pancreas which acts in a purely catalytic manner on the vital destruction of sugar.

#### The Islets of Langerhans.

By perhaps the majority of authors the pancreas is considered to consist of two separate and distinct kinds of tissue, the secreting alveoli, and the islets of Langerhans. The question, however, as to the morphology and physiology of the islets of Langerhans needs a little discussion. Modern writers may be divided into two chief groups according to their views as to the morphological significance of the islets. The first of these believe that the islets are essentially of the same embryological and morphological nature as the zymogenous tubules, and are not to be looked upon as, in any sense, organs *sui generis*. The second group of

observers regard the structures in question as definite and distinct organs, analogous to the cortex of the adrenal, the epithelial part of the pituitary body, and the parathyroids, and consider that they have no connection (except a community of embryonic origin) with the secreting tubules of the pancreas.

Some recent contributions on the subject are in support of the view that the islets are organs *sui generis*, and this notwithstanding that, in the view of the present writer, the balance of evidence is now overwhelmingly against this hypothesis. In the handbooks, too, the islets are usually considered as a separate kind of tissue.<sup>1</sup> Kohn (184) also classifies the islets of Langerhans as one of his "Drüsen ohne Ausführungsgang—ohne Drüsenlumen" ("corpora glanduliformia") along with the parathyroids, the epithelial part of the pituitary, and the cortex of the adrenals.<sup>2</sup>

Some among the first group of writers even consider there may be no difference *in function* between the two structures. Thus Harris and Gow (156) thought that the islets might take part in the external secretion, probably forming one of the ferments. Jarotzky (174) believes that they may take part in both an internal and an external secretion. Lewaschew (213) and Pischinger (290) look upon the islets as exhausted secreting cavities, and believe that after a period of repose they may again take on their secretory function. Tschassownikow (367) and Dogiel (77), on the contrary, look upon the islets as exhausted acini which are unable to return to their former state. It will be seen that the four last-named observers hold a view not widely differing from that of Laguesse, Dale, and Vincent and Thompson.

Statkewitsch (355) looks upon islets as alveoli modified

<sup>1</sup> Thus v. Ebner (85) says: "Durch die sorgfältigen Untersuchungen von Laguesse über die histogenetische Entwicklung der Bauchspeicheldrüse des Schafes ist nachgewiesen, dass die Langerhansschen Zellenhaufen derselben entodermalen Anlage hervorgehen, wie die secernierenden Schläuche. Doch kann man nach dem histologischen Befunde an den ausgebildeten Zellenhaufen dieselben nicht zu dem eigentlich secernierenden Parenchym rechnen, da Sekretwege, trotz gegenteiliger Angaben von Lewaschew, in denselben nicht nachzuweisen sind. Die Langerhansschen Zellenhaufen scheinen mir vielmehr einige Ähnlichkeit mit gewissen Blutgefäßdrüsen wie die Nebenniere, der vordere Lappen der Hypophyse usw. zu haben."

<sup>2</sup> It has been shown, however, that the parathyroid is very intimately related, physiologically and histologically, with the thyroid gland. [Vincent and Jolly (377, 378), Halpenny and Thompson (152), Thompson (364), Halpenny (151).]

by inanition, and Mankowski (234, 235) emphasizes to the full the intimate relation subsisting between islets and tubules, their functional variations and forms of transition, but does not appear to have committed himself as to their function.<sup>1</sup>

In most vertebrates there are no lumina in the islets of Langerhans. But Gianelli and Giacomini (123) described lumina in the islets of reptiles, and, although Gianelli seems later to have developed doubts upon this point (122), yet their existence has been fully confirmed by Laguesse (188-194), and by Perdrigeat and Tribondeau (279). Laguesse (*loc. cit.*) has given very convincing illustrations of his results on this point obtained by Golgi's method. Dale (66) has also described lumina within the islet area in the toad.

Laguesse refuses to admit that the islets are simply exhausted masses of acini, or that they are in their nature simply secreting tubes modified by inanition, and he urges against either of these theories the abundance of the granules of secretion in the islets, the permanent juxtasplic islet of the Ophidians, and the fact that islets are found in every functional state of the pancreas. The presence of lumina in the islets of reptiles is a strong indication that their origin is from alveoli. The same author, in his numerous contributions on the subject, has laid stress on the anatomical details above referred to, and inclines strongly to the view that the islets of Langerhans are portions of the secreting tubules temporarily modified for the purpose of supplying an internal secretion.

Dale (66) employed a new method for investigation of the subject, using secretin [Bayliss and Starling (16, 18)] to exhaust the gland. He concluded that the islets of Langerhans are not independent structures, but are formed by certain changes in the cells of the secreting tissue of the pancreas. The change from the secreting to the "islet" condition may be accelerated by the administration of secretin and as a result of inanition.

The authors belonging to the second chief group all believe in the internal-secretion theory of the islets, and, indeed, so convinced are many of them that this is the

<sup>1</sup> Mankowski's full paper (235), the contents of which have been gleaned from the extract in 234, is beautifully illustrated.

correct theory, that they refuse to admit the statements of the first group, who describe changes in the islet in exhaustion and inanition, and the transition forms from one kind of tissue to the other. The chief upholders of this "separate-organ" view of the islets are Diamare (73), Rennie (309), Massari (244), and Helly (162), among comparative anatomists, and Ssobelew (350), Opie (266, 267, 268), and others among pathologists. According to Diamare, the islets are "epithelial bodies" in Kohn's (184) sense. They are constant and invariable, and are a form of "epithelial body" derived from the pancreas (for he admits, of course, the common embryonic origin of pancreas and islets). The adult islets, in his view, have no relation to the surrounding tissue, except that of contiguity, and he denies that the islets ever possess lumina, even in reptiles. He denies the continuity of the islets with the exocrine gland and all forms of physiological variation. Rennie, in his work on the teleostean fishes, describes the fairly constant occurrence of an encapsuled islet ("principal islet") of large size, whose relation to the pancreatic tissue is frequently extremely slight. He considers the islets to be "blood-glands" which have entered into a secondary relation to the pancreas. This author finds no sign of any transitional forms. Helly also believes that the islets are organs *sui generis*, and denies the existence of any form of transition. Pensa (277, 278) finds a very abundant vascular and nervous supply to the islets of Langerhans, and in his opinion these structures present certain peculiarities. These will not allow him to believe either that the islets are rudimentary organs, or that they are even modified portions of the zymogenous tissue of the pancreas.

The present writer, as the result of investigations carried out in conjunction with Mrs. Thompson, is opposed to the views of these latter authors, and considers that the embryological work of Laguesse and the experimental researches of Dale are confirmed in all essential points. Diamare (73), in his most recent communication, still holds to his original view. He only refers to Dale's work in a footnote, and neither he nor any other observer (previously to the work of Vincent and Thompson) has, so far as I am aware, repeated Dale's experiments upon the mammalian



pancreas. Diamare has, it is true, done some experiments upon fishes, but with negative results. It is, of course, remotely possible that in fishes the islets are constant structures, while in the other vertebrates they are variable; but one would certainly hesitate at present to adopt such a view. It is remarkable that Diamare has been unable to see the various transition forms which are figured for

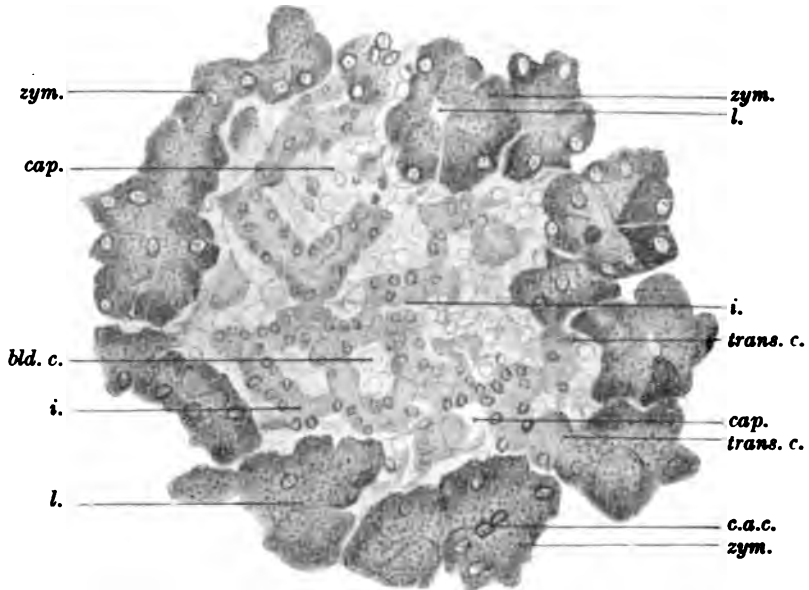


FIG. 10.—Islet of Langerhans, from the splenic end of the pancreas of a normal dog, showing the alveolar form of the islet tissue. The tissue of the islet is seen to consist of solid branching columns of cells, for the most part two deep, separated by wide capillary bloodvessels (Vincent and Thompson). (Drawn by Mrs. F. D. Thompson.)

Lettering common to Figs. 10, 11, and 12.—*bld. c.*, red blood-corpuscles; *c.a.c.*, centro-acinar cells; *cap.*, blood-capillaries; *i.*, islet of Langerhans; *l.*, lumen; *trans. c.*, transitional cells; *zym.*, zymogenous tissue.

different animals by various observers—namely, Mankowski, Laguesse, Dale, and Vincent and Thompson (381, 382, 383).

The accompanying illustrations, taken from the paper by Mrs. Thompson and the present writer, will illustrate some of the points under discussion. Fig. 10 represents an islet of Langerhans from the splenic end of the pancreas of a normal dog, showing the “alveolar” form of the islet

tissue. The islet is seen to consist of solid, branching columns of cells, for the most part two deep, separated by wide capillary bloodvessels. In some places the zymogenous tissue shows transitions towards islet. Fig. 11 is a section taken from the splenic end of the pancreas of a normal pigeon. The section shows the islets and the zymogenous tissue. Compare this with Fig. 12, which shows the splenic end of the pancreas of a pigeon after a few days' inanition. The increase in the amount of islet tissue is very striking.

Rennie's "principal islet" is, it must be admitted, a



FIG. 11.—From the splenic end of the pancreas of a normal pigeon. The section shows the islets and the zymogenous tissue. Compare this with the next figure (Vincent and Thompson). (Drawn by Mrs. F. D. Thompson.)

Lettering same as for Fig. 10.

very interesting occurrence, and its frequent presence can be verified in quite different species from those examined by Rennie. But it cannot be admitted that it carries the significance attached to it by this author. The fact that the teleostean islets are so often encapsuled loses much of its importance when it is pointed out that isolated portions of the zymogenous tissue are also frequently encapsuled. Lewaschew (213), as the result of injection experiments, found in some cases lumina in the islets of mammals. Dogiel (77), on the other hand, using Golgi's silver-chromate impregnation, was unable to confirm this, and explained

Lewaschew's results as being due to the extravasation of the injected material. But Laguesse, using the same method, found in the islets of the snake lumina in perfect continuity with those of the acini, and his plates show an admirable figure illustrating this. He considers, in fact, that in reptiles there are, strictly speaking, no solid cords at all, but only columns of cells in which the lumen has become effaced. In *Kinosternon* in some of the islets Mrs. Thompson and the present writer were able to find distinct lumina, but

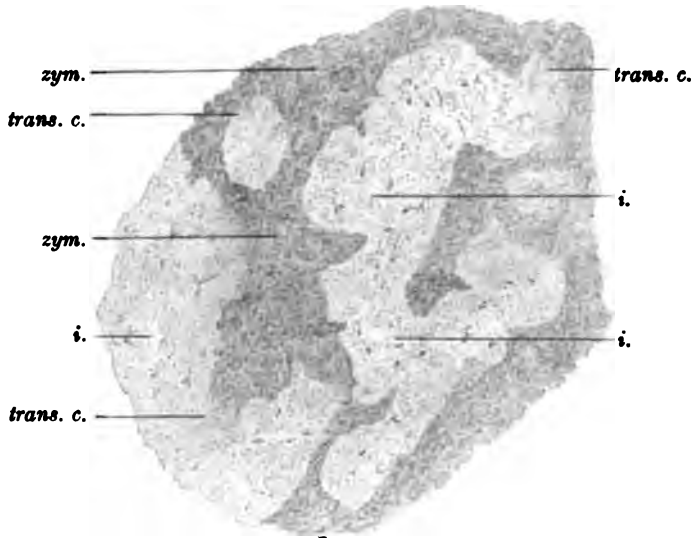


FIG. 12.—Splenic end of the pancreas of a pigeon after a few days' inanition. The increase in the amount of islet tissue is very marked (Vincent and Thompson). Cf. with Fig. 11. (Drawn by Mrs. F. D. Thompson.)

Lettering same as for Fig. 10.

could not trace their connections with the lumina of the acini. In *Amia calva*, too, lumina were detected in the islet tissue.

If a pancreas from an animal in inanition is examined, a very remarkable increase in islet tissue is noted (see Figs. 11, 12), but if after such a period the animal is restored to its normal state of nutrition, the usual proportion of islet tissue is found. The most obvious explanation of this is that the alveoli are reformed from the islet tissue. There is, however, another possibility—namely, that the islet tissue

formed from alveoli, as a result of changed physiological conditions, is not reconverted into secreting tubules, but, having reached the last stage of its career, degenerates and disappears. If this be the case, we must assume that new alveoli are formed from the existing tubules, and occupy the space recently occupied by islets. On this hypothesis the more solid islets might be regarded as nothing more than worn-out alveoli about to disappear. Of the two possible views here put forward, the present writer is inclined to support the former.

Experiments involving ligation of the pancreatic duct have given contradictory results in the hands of various observers, but, on the whole, the balance of evidence derived from this line of investigation is in favour of the view that "islet" is not a kind of tissue separate and distinct from "alveolus." According to Ssobolew (350) and Schultze (333), ligation of the duct is followed by a complex atrophy of the pancreatic cells proper, while those of the islets of Langerhans are not affected; and these statements have been urged in favour of the view that the islets are functional entities, independent of zymogenous tissue. But other observers—notably Mankowski (234, 235) and Dale (66)—deny that the islets in the pancreas show any special immunity from the destructive effects of the operation, though Laguesse believes that, under these conditions, many islets are newly formed by budding from the ducts; and Dale is of opinion that much of the tissue escaping destruction assumes a form resembling the islets.

Lépine (204, 206, 207, 208, 209, 210) has shown that injection of oil into the duct of Wirsung, or even a simple ligation, is followed by an increase in the glycolytic power of the blood. But he does not believe that this blood change is due to any action upon the islets of Langerhans. Lombroso (222-225) recently reports that in dogs and pigeons complete occlusion of the ducts produces no marked effect upon the pancreatic tissue. He admits that, in addition to the external secretion, the pancreas has some other function which persists even when the external secretion is abolished. But he seems inclined to attribute this not specially to the islets of Langerhans, but to the general parenchyma of the gland.

Schäfer (323, 325) was the first to suggest that the islets of Langerhans are the part of the pancreatic tissue concerned with carbohydrate metabolism. A number of more recent observers [Opie (266, 267, 268), Ssobolew (350), Herzog (170), Weichselbaum<sup>1</sup> and Stangl (394, 395), and Gentès (120)] have found in cases of diabetes mellitus that the islets are affected by a hyaline degeneration, atrophy, or inflammatory changes; but Kasahara (176), Wright and Joslin (407), v. Hansemann (155), Dieckhoff (75), Schmidt (329), and Gutmann (139) have been unable to confirm these results. Notwithstanding the conflicting nature of the evidence upon this point, a large number of pathologists have—at any rate, until quite recently—appeared to favour the view that the islets of Langerhans constitute a tissue *sui generis*, whose function it is to control, by means of some kind of internal secretion, the metabolism of sugar in the body.

Diamare (71, 72, 73, 74) has, indeed, put forward some experimental work in support of this definite view as to the function of the islets. He finds that the amyolytic ferment occurs only in the ordinary pancreatic cells, while it is absent in the islets of Langerhans. He states that the islets possess the power of inverting grape-sugar, and is of opinion that these structures are intimately concerned in the economy of glucose in the body. The glycolytic action of the islets *in vitro* is very weak, and he looks upon the tissue as furnishing an endocrine zymoplastic secretion. Hyperglycæmia and diabetes are in this view the result of functional insufficiency of the islets. This observer further records certain modifications occurring in the islets of *Motella tricirrata* as the result of the injection of glucose into the abdominal vein.

As we have seen, the present writer, working in conjunction with Mrs. Thompson, was the first to prove experimentally that the islets of Langerhans actually pass through a structural cycle, corresponding to a cycle of changes in physiological conditions. We were able to provoke experi-

<sup>1</sup> Weichselbaum (392, 393) has recently returned to the subject, and has published the results of the investigation of 183 cases of diabetes, in which a post-mortem examination was made. He is decidedly of opinion that the essential pathological change in diabetes is in the islets of Langerhans. These papers, especially 393, give a very full account of the literature up to date.

mentally the formation of new islets at the expense of the exocrine parenchyma, and then to induce their disappearance by a new transformation into acini.

Laguesse (194), working with the pigeon, has quite recently been able to confirm our results. He has performed a very large number of experiments, and his results are carefully tabulated. He gives, moreover, a careful account of the anatomy of the pancreas in the pigeon. He states his conclusions as follows: "Chez les animaux soumis à l'inanition pendant quelques jours, le nombre des îlots double presque, pour retomber à son taux normal chez les pigeons renourris." "Nos observations, complétant et élargissant celles de Swale Vincent et Thompson, nous paraissent fournir une preuve expérimentale très démonstrative du balancement."<sup>1</sup>

This view has now at last been accepted by some modern writers of textbooks. Adami (3) affirms that he has encountered appearances in the human subject which would be difficult to explain, except on the hypothesis that the islands are not separate organs; that they vary in number according to the state of nutrition and activity of the gland, becoming converted into active acini, and *vice versa*. As Adami justly points out, these observations do not wholly negative the contention that the islands bear some intimate relationship to a certain order of cases of diabetes; they suggest, however, that degenerative changes seen in them are an indication of other changes occurring in the intimately connected pancreatic tissue proper.

Whatever may be subsequently discovered to be the true function of the islets of Langerhans, their intimate anatomical relationship with the zymogenous tubules, the numerous transition forms in all groups of vertebrates, and the transformation of alveolus into islet, and *vice versa*, all appear to prove conclusively that the islets are not organs *sui generis*, but are an integral part of the pancreatic tissue. As to whether the temporary structural modification of

<sup>1</sup> M. Labbé and P. Thaon (187) have recently reported an increase in amount of islet tissue in guinea-pigs when fed on animal food. This seems probably due to inanition. Bensley (*Amer. Journ. of Anat.*, vol. xii., 1911), as the result of very careful work, finds himself unable to agree with Vincent and Thompson, but Fischer (*Archiv. f. mikr. Anat.*, 79, 1912) reaches the same conclusions as ourselves.

alveolus into islet tissue corresponds to a specialization of function, the evidence is at present inconclusive.

A prolonged discussion of the pathology of glycosuria and of the precise manner in which the internal secretion of the pancreas normally prevents such a condition, would serve no useful purpose. It is, however, of supreme medical importance to bear in mind that a certain order of cases of diabetes mellitus are, in all probability, due to insufficiency of the internal secretion of the pancreas. But we must bear in mind the possible influence of disturbances in certain others of the ductless glands which are concerned with carbohydrate metabolism, as, for example, the adrenal and the thyroid.<sup>1</sup> In the meantime the question as to the precise relationship between various forms of glycosuria and disease of the pancreas can only be answered by renewed and long-continued investigation on the part of physicians and pathologists.

A functional relationship between the islets of Langerhans and the reproductive organs is claimed by Rebendi (305), and a similar relationship between the spleen and the pancreas has been suggested by certain authors. Rettger (310) reports that intravenous injection of watery extracts of spleen into spleenless dogs raises the trypsin contents of the pancreas.<sup>2</sup>

<sup>1</sup> Other papers bearing upon this part of the subject are: Gentès (121), Lüthje (230), Zunz und Mayer (408, 409), Lorand (227), Glaessner u. Sigel (125), Küster (186), Dewitt (70), Heiberg (159).

<sup>2</sup> See, however, Mendel and Rettger (245), Camus and Gley (49), A. Frouin (114).

## CHAPTER VII

### THE INTERNAL SECRETION OF THE KIDNEY

A BELIEF in some kind of internal secretion on the part of the kidney has existed since the period when interest in the subject was stirred by the researches of Brown-Séquard. We have already seen (p. 33) that some writers [Tigerstedt and Bergman (365), Vincent and Sheen (379, 380), and Batty Shaw] have described pressor effects as the result of the injection into animals of extracts made from the kidney. Lewandowsky (211), however, found that with 5 to 6 centimetres of the blood from the renal vein no more positive result upon the blood-pressure was obtained than with a similar amount of blood taken from any other vein in the body. He concludes that no specific pressor substance is poured out from the kidney by the renal vein. The present writer has frequently tested the effects of different kinds of kidney extracts upon the blood-pressure. Sometimes there is a slight rise of pressure, sometimes there is no rise, or there may be a fall. The rise is never very marked, and only occurs with unboiled "protein" extracts. The same result may frequently be obtained from extracts made from other organs and tissues [Vincent and Sheen (379, 380)], and it may probably be concluded that, so far as the question of internal secretion is concerned, the results are not of any great importance. Further, it may be stated as probable that the high blood-pressure and hypertrophy of the heart in nephritis bear no relation to the presence of a pressor substance in kidney extracts.

But arguments based upon experimental work of a different character and upon clinical and therapeutical observations have been urged in favour of the view that the kidneys furnish an internal secretion. Brown-Séquard (38),



in 1869, had expressed the opinion that the phenomena of uræmia were not entirely due to the accumulation of urinary constituents in the blood, but to the absence of the normal internal secretion, or, as he expressed it, due to "l'existence de changements chimiques morbides du sang remplaçant la sécrétion interne normale." This view was partly based upon clinical observations in which in spite of long-continued anuria the symptoms of uræmia were practically absent. Later, in 1892, Brown-Séquard and d'Arsonval (43, 44) stated that "le rein a une sécrétion interne d'une grande utilité." They removed both kidneys from rabbits and guinea-pigs, and found that death occurred much earlier than after ligature of both ureters, although, of course, in both cases there was an accumulation of urinary substances in the blood. Then they administered to some of these by subcutaneous injection diluted juice of kidney from a normal animal of the same species, while they left others untouched as controls. They found that those animals which had received the injection survived one or two days longer than the controls; the duration of life in the injected animals was, in fact, equal to or longer than that of animals which had undergone ligature of both ureters. The phenomena of uræmia were of slower development in those animals which survived the longer, owing to treatment with kidney extract.

Some observations of Lépine (203, 205) seemed to point to the fact that the kidney blood contains peculiar substances. Working with rabbits, this observer found that tying both ureters induced death after fall of temperature, vomiting, and diarrhœa. But if the flow through the ureter were checked by connecting it with a vessel containing normal saline at a higher pressure than that in the ureter, then the symptoms induced were quite different. Instead of a fall of temperature there was a rise, and in addition one observed increased rate of respiration and convulsions. A watery extract of kidney injected into the circulation produces, according to Lépine, a rise of temperature and dyspnœa. He concludes that the kidney substance contains materials inducing these effects, and suggests the possibility of auto-intoxications of renal origin.

E. Meyer (246), a pupil of Brown-Séquard, found that while

the blood of uræmic animals produces no definite effects upon normal animals, when injected into nephrectomized animals, it induces dyspnoea and slowing of respiration. The same observer further found (247) that injections of kidney extract, or normal blood, or of renal venous blood from a normal animal, have the immediate effect of checking the Cheyne-Stokes respiration which is such a striking symptom of uræmia.

Vitzou (384) found that in rabbits and dogs the injection subcutaneously and intravenously of defibrinated blood from the renal vein of a normal animal prolonged the life of a nephrectomized animal in a very striking manner. Thus in one rabbit the survival was forty-two and a half hours longer than was the case with the control, which had, like the first, undergone double nephrectomy. Vitzou concludes that the kidney has an important internal secretion, the absence of which plays an important part in the causation of uræmia.

Many experiments of a similar character have been performed [E. Vanni et Manzini (371), Ajello and Parascandolo (4), Mori (257), Bozzoto (36), Gilbert and Carnot (124), Spineanu (349), Maragliano (236), Chatin and Guinard (56), Fiori (91, 92, 93, 94)]. Some of these have been in favour of the views expressed by Meyer and Vitzou, some have been opposed to it. The results obtained have been in fact very contradictory. Thus Chatin and Guinard (56) investigated the question as to whether, by injection of blood from the renal vein of normal dogs into nephrectomized animals, there was any lengthening of life, or a diminution of the uræmic symptoms. The results were completely negative—that is to say, the animals treated with the serum died on the whole sooner than those not treated. Chatin and Guinard do not, however, definitely deny an internal secretion on the part of the kidney, for which they think there is a certain amount of clinical evidence.

It is doubtful if much importance can be attached to the results obtained by Vitzou. His work has been severely criticized by Lewandowsky (212), who points out that as a matter of fact animals can live from three to five days after double nephrectomy; whereas Vitzou states that he succeeded by his treatment in causing them to live sixty to

sixty-nine hours instead of thirty-four! As pointed out by Biedl (25), the duration of life of nephrectomized animals is extremely variable. According to his own experiences in some cases dogs and rabbits may survive as long as five or six days after extirpation of both kidneys, while in other cases they may die in thirty-six hours. Again, the incidence and course of the symptoms of uræmia in such animals is no criterion of their actual condition. It frequently happens that nephrectomized animals show no characteristic symptoms for two, three, or even four days, and then suddenly succumb. Others, on the other hand, on the day after the operation, suffer from vomiting and dyspnœa, then either recover or remain in a chronic condition of uræmia for several days [Biedl (25)]. Such experiments are of little value as demonstrating an internal secretion on the part of the kidney, and still less as pointing to the treatment of nephritis in man by means of kidney extracts. However, Capitain (50) reports a case of severe uræmia cured by subcutaneous injections of kidney extracts. Teissier and Frenkel (363) state that injection of kidney extracts relieved nephritis, and Formanek and Eiselt (110) report good results in five cases of chronic nephritis after treatment with kidney extracts by the mouth.

Rautenberg (306) performed a series of experiments upon rabbits, in which he tied one (the left) ureter. The ligature was removed at the end of three weeks, and later the healthy (right) kidney was extirpated. The animal lived with the diseased kidney for one and a half to two and a half years, and suffered from albuminuria, high blood-pressure, and other signs of nephritis. At the autopsy there was found to be extensive artero-sclerosis.

Lindemann (215) found that guinea-pigs, after having received injections of rabbit-kidney emulsions, furnished a serum which was very toxic to rabbits, giving rise to albuminuria and uræmia. The injection of this nephrolytic serum provokes symptoms precisely similar to those induced by true kidney poisons. Here we have the formation of certain specific substances formed in the blood under the influences of the processes of absorption of the renal substance injected, and these are the substances which affect the kidney. Schültze (332) could not observe the

nephrotoxic effect of the serum of rabbits into which he had injected an emulsion of guinea-pig kidney. This observer also could not confirm the hepatolytic effect of the sera of animals which had been injected with liver emulsion, although Delezenne and Deutsch (69) affirm that animals into which one injects liver emulsions furnish a serum which possesses powerful hepatotoxic properties.

Néfédieff (261) believes firmly in a specific nephrotoxic serum in Lindemann's sense. He states further that this serum is also hæmolytic. The serum is analogous to the cytotoxines in general. Under the influence of hypodermic injections of kidney emulsion from healthy animals there appear in the blood of rabbits and guinea-pigs certain substances which exercise an injurious effect on the kidneys of the species of animal whose organs have been used in the preparation of the emulsion. Néfédieff found also that the serum of rabbits in which one of the ureters had been tied soon acquires powerful nephrotoxic powers. He suggests that in this case substances pass from the kidneys into the blood just as they do when an emulsion of the kidney has been injected.

Arguments of an analogous kind have also been used to explain the causation of œdema in nephritis. Kast (177) observed that the blood of nephritics with œdema contains a lymphagogue substance of great strength, which also passes out into the dropsical fluid. Blanck (28) noted, in investigating the serum of animals with uranium nephritis and uranium œdema, and of rabbits with chromium or aloin nephritis (which does not give rise to œdema), that if one injects rabbits with serum or œdematous fluid from a rabbit affected with uranium nephritis, one gets œdema in this case also. Timofeen (366), from a review of the work of previous experimenters and on the basis of his own investigations, believes that the cause of the œdema in nephritis is the passing into the blood of certain lymphagogue substances, the source of which is a substance he calls "nephroblaptine" arising in the diseased kidney.

A discussion of this question would not be complete without a reference to the work which has been carried out upon the influence of the kidney on metabolism. Sir J. Rose Bradford (37) removed portions of the kidney from

animals, and subsequently studied their metabolism. He obtained results which suggested that when the amount of available kidney substance is greatly reduced the tissues of the body, and more especially the muscles, rapidly break down and liberate urea. But he states that he has no observations to show whether this is dependent upon the cessation of the action of an internal secretion supplied normally by the kidney.

Biedl (25) performed a series of experiments of a similar nature upon dogs. He excised wedge-shaped pieces of the kidney, removing about a quarter of a kidney, and sometimes removed the whole of the other kidney in addition. It was found that after such operations the quantity of urine secreted was notably increased, even up to two, three, four, or five times the original amount. At the same time the total nitrogen excreted was much increased. V. Haberer (140) also reports polyuria after excision of portions of the kidney substance. It is not possible to state whether these changes are really due to a deficiency in a normal process of internal secretion on the part of the kidney. Suñer (359, 360) is definitely opposed to the view that the kidney provides any internal secretion.

## CHAPTER VIII

### THE INTERNAL SECRETION OF THE INTESTINAL MUCOUS MEMBRANE AND THE NORMAL MECHANISM OF THE SECRETION OF THE PANCREATIC JUICE

It was first observed by Claude Bernard that the secretion of the pancreatic juice is dependent on the passage of food into the duodenum, and it has long been known that in the dog the flow of pancreatic juice, although it begins immediately after food has been taken, does not reach its maximum till either the first or the second hour, but more commonly is not reached until the third or fourth hour. It is to be noted that this is at a time when the greatest quantity of food from the stomach contents is passing into the duodenum. There has been much laborious investigation and a continued keen controversy as to the causal relationship existing between the passage of food through the pylorus and the secretion of pancreatic juice.

It will be interesting to take a glance at the state of knowledge on this subject in the year 1889. This can be conveniently done by recalling the expositions in a standard textbook of the period. M. Foster (111) says: "Stimulation of the medulla oblongata or of the spinal cord will call forth secretion in a quiescent gland, or increase a secretion already going on. From this we may infer the existence of a reflex mechanism, though we cannot as yet trace out satisfactorily the exact path of either the afferent or the efferent impulses; all we can say is that the latter do not reach the pancreas by the vagus, since stimulation of the medulla is effective after the section of both vagi.

"A secretion already going on may be arrested by stimulation of the central end of the vagus, and the stoppage of the secretion which has been observed as occurring during and after vomiting is probably brought about in this way.

This effect, which, however, is not confined to the vagus stimulation of other afferent nerves, such as the sciatic, producing the same effect, may be regarded (in the absence of any proof that the result is due to reflex constriction of the pancreatic and local vessels unduly checking the blood-supply) as an inhibition of a reflex mechanism at its centre in the medulla or in some other part of the central nervous system, much in the same way as fear inhibits at the central nervous system the secretion of saliva following food in the mouth. But if so, then we must regard the secretion of pancreatic juice as closely resembling that of saliva, inasmuch as it is called forth by a reflex act. Yet it is stated that, unlike the case of saliva, the secretion of pancreatic juice continues after all the nerves going to the gland have been divided, an operation which would do away with the possibility of reflex action. Such an experiment, however, cannot be regarded as decisive, since it is almost impossible to be sure of dividing all the nerves."

It is interesting to note how the one single observation (secretion after severance of all nerves), which at this period had to be opposed to the theory of reflex stimulation, was dealt with by Michael Foster. At this date, then, and for some time later the prevailing view was that the flow occurring when the acid chyme passed into the duodenum is due to the action of a reflex arc; but the observations of Bernard (21), Heidenhain (160), and Pawlow (274), incorporated in the above account by Foster, were inconclusive, and the results obtained in different experiments were by no means constant. In more recent years Pawlow and his pupils (272, 273, 275) have multiplied ingenious experiments and developed a wonderful technique, have struggled hard to reconcile the conflicting statements of different observers, and with infinite ingenuity have sought to establish on a firm basis the theory of nervous action. In searching for the channels of the reflex, Pawlow showed that, if certain precautions be taken, one can bring about a flow of pancreatic juice by stimulating the vagus or splanchnics.

A great step in advance was made by Popielski (294, 298), and by Wertheimer and Le Page (396, 397, 400, 401, 402, 403, 404). These observers proved conclusively that intro-

duction of acid into the duodenum still excites pancreatic secretion after section of both vagi and both splanchnic nerves or destruction of the spinal cord, or even after complete extirpation of the solar plexus. Thus it was clear that ordinary reflex action was out of the question. Popielski concluded, therefore, that the secretion is due to a local, a peripheral, reflex action, the centres for which are situated in the scattered ganglia found throughout the pancreas.

Wertheimer and Le Page, however, made a very interesting discovery—namely, that secretion of the pancreatic juice could also be induced by the injection of acid into the lower portions of the small intestine, the effect, however, gradually diminishing as the injection was made nearer and nearer the lower end of the small intestine, so that no effect at all was produced from the lower two feet of the ileum. Secretion could be excited from a loop of jejunum entirely isolated from the duodenum. Wertheimer and Le Page conclude that, in this latter case, the reflex centres are situated in the ganglia of the solar plexus, but they did not perform the obvious control experiment of injecting acid into an isolated loop of jejunum after extirpation of these ganglia.

About this time Bayliss and Starling were engaged upon investigations into the local nervous reflexes concerned with movements of the intestine. These observers made numerous experiments to test the validity of a hypothesis such as that of Wertheimer and Le Page, but soon found that in the case of the pancreatic secretion they were dealing with an entirely different order of phenomena, and that the secretion of the pancreas is normally called into play, not by nervous channels at all, but by a chemical substance which is formed in the mucous membrane of the upper parts of the small intestine under the influence of acid, and is carried thence by the blood-stream to the gland cells of the pancreas.

The experiments of Bayliss and Starling (14, 15, 16, 18) confirmed those of previous observers in so far as they found that, after exclusion of all nerve centres except those in the pancreas, a secretion of pancreatic juice is obtained by the introduction of acid into the duodenum. But, as pointed



out above, the *experimentum crucis* of taking an isolated loop of intestine, dividing the mesenteric nerves supplying it, and then injecting acid into it, had not been performed. This crucial experiment is best described in the words of the authors :

“ On January 16, 1902, a bitch of about 6 kilos weight, which had been fed about eighteen hours previously, was given a hypodermic injection of morphia some three hours before the experiment, and during the experiment itself received A.C.E. in addition. The nervous masses around the superior mesenteric artery and coeliac axis were completely removed, and both vagi cut. A loop of jejunum was tied at both ends, and the mesenteric nerves supplying it were carefully dissected out and divided, so that the piece of intestine was connected to the body of the animal merely by its arteries and veins. A cannula was inserted in the large pancreatic duct and the drops of secretion recorded. The blood-pressure in the carotid was also recorded in the usual way. The animal was in the warm saline bath, and under artificial respiration.

“ The introduction of 20 c.c. of 0.4 per cent. HCl into the duodenum produced a well-marked secretion of one drop every twenty seconds, lasting for some six minutes ; this result merely confirms previous work. But—and this is the important part of the experiment, and the turning-point of the whole research—the introduction of 10 c.c. of the same acid into the enervated loop of jejunum produced a similar and equally well-marked effect.

“ Now, since this part of the intestine was completely cut off from nervous connection with the pancreas, the conclusion was inevitable that the effect was produced by some chemical substance finding its way into the veins of the loop of jejunum in question, and being carried in the blood-stream to the pancreatic cells. Wertheimer and Le Page have shown, however, that acid introduced into the circulation has no effect on the pancreatic secretion, so that the body of which we were in search could not be the acid itself. But there is between the lumen of the gut and the absorbent vessels a layer of epithelium, whose cells are, as we know, endowed with numerous important functions. It seemed, therefore, that the action of acid

on these cells would produce a body capable of exciting the pancreas to activity. The next step in our experiment was plain—viz., to cut out the loop of jejunum, scrape off the mucous membrane, rub it up with sand and 0.4 per cent. HCl in a mortar, filter through cotton-wool to get rid of lumps and sand, and inject the extract into a vein. The first effect is a considerable fall of blood-pressure . . . and, after a latent period of about twenty seconds, a flow of pancreatic juice at more than twice the rate produced at the beginning of the experiment by introduction of acid into the duodenum.”

Bayliss and Starling suggest the name “secretin” for the active substance present in the intestinal extract, and the term has been adopted by subsequent workers. Secretin is probably produced by a process of hydrolysis from a precursor “prosecretin” present in the intestinal cells. It is not a ferment, nor is it of the nature of an alkaloid or diamino-acid.

The results obtained by Bayliss and Starling were confirmed by Camus and Gley (45, 46, 47), Borissow and Walter (29), Delezenne (68), and Stassano and Billon (354), and Wertheimer (398, 399) demonstrated the presence of secretin in the blood flowing from a loop of intestine into which acid has been introduced.

In a later communication (18) Bayliss and Starling announced that secretin can be prepared from the upper part of the intestine of any animal belonging to the class of vertebrata by scraping off the mucous membrane, pounding it up, and boiling with dilute hydrochloric acid.

The experimental evidence which is clearly put before us by Bayliss and Starling justifies the view that the normal sequence of events in the secretion of juice by the pancreas is as follows: The acid of the gastric juice upon reaching the duodenum converts the prosecretin manufactured by the epithelial cells into secretin; this secretin is then absorbed into the blood-stream, carried to the cells of the pancreas, and stimulates the organ to secretory activity. *The external secretion of the pancreas is the result of the internal secretion of the duodenal mucous membrane.*

The formation of prosecretin in the duodenum does not appear to take place as a response to the stimulus of ingestion

of food. Pringle (304) has quite recently found that secretin prepared from newly-born kittens, before suckling, gives a fairly active flow of juice when tested on a dog. When foetuses of different periods were examined, it was found that some showed the presence of an active secretin, some did not. Further experiments are being carried out with the object of determining whether there is any definite correlation between the period of development and the appearance of secretin in the duodenal mucous membrane.

In this most important discovery of Bayliss and Starling is involved an important modification of our conception as to the empire of the nervous system. The production of secretin is, in fact, the best authenticated example of internal secretion which can be quoted. The hitherto most oft-cited examples, such as those of the adrenal body and the thyroid gland, are, in the opinion of the present writer, more distinctly hypothetical.

Beyond all doubt secretin is a powerful excitant of the pancreatic secretion, but its specific nature is denied by some authors. Bayliss and Starling admit that secretin acts to a small degree on the secretion of bile,<sup>1</sup> and other authors [v. Fürth and Schwarz (116), Frouin (115)] state that it acts on the secretion of saliva and the gastric and intestinal juices. Again, while Bayliss and Starling (16), Falloise (90, 96, 97), and Hallion and Lequeux (150) affirm that secretin can only be obtained from the upper part of the small intestine, Delezenne (68) and Frouin (115), Camus (46), and Camus and Gley<sup>2</sup> (47) found this substance, though only in small amount, in other parts of the intestinal tract, and even in lymphatic glands. Popielski (295, 296, 297, 299) states that he obtained secretin from the stomach and from the large intestine.

Although Bayliss and Starling showed that the depressor substance in extracts of the intestinal mucous membrane is independent of secretin, and that a secretin solution can be obtained free from the depressor substance, yet this has not hindered Popielski and others from urging that the flow of pancreatic juice after injection of intestinal extracts

<sup>1</sup> See also Henri and Portier (165).

<sup>2</sup> Gley has quite recently (127) reported that a powerful stimulant to the pancreatic flow can be obtained by maceration of the duodenal mucous membrane with solutions of albumose.

is due to the lowering of the blood-pressure and consequent anæmic stimulation of nerve centres.

Fleig (98, 99, 100, 101, 102) shows that secretin does not produce its effects by acting on the nerve endings in the intestinal epithelium, and the last-named author, as well as Wertheimer and Le Page, state that they obtained a secretion of pancreatic juice by injecting acid into an isolated loop of jejunum whose nerve communications were intact, and even when the venous blood of this loop is diverted, and the thoracic duct is tied off. Fleig concludes that the mechanism of secretion of pancreatic juice after the injection of acid into the upper part of the small intestine is, under normal conditions, of a double character: (1) Secretin calls forth secretion of pancreatic juice by direct action on the cells of the pancreas. (2) Acids, independently of the formation of secretin, cause a secretion of pancreatic juice by reflex nervous action.

In regard to the chief points under discussion, it is worth noting that, apparently, where most experiments upon the subject have been performed, there the views of Bayliss and Starling are accepted, and in such matters a few carefully conducted experiments are of more avail than endless reading and discussion.

V. Fürth and Schwarz (116) believe that secretin is not a definite, single substance, but a mixture of several gland-stimulating substances, of which choline can be recognized as one.

With regard to the mechanism of the secretion of the intestinal juice, nothing definite is yet known. We know that the juice when it is formed is essential for the activation of the pancreatic juice by means of the enterokinase. The trypsinogen is only converted into the proteolytic ferment trypsin after the action of the enterokinase. According to Pawlow, the secretion of the succus entericus depends upon two factors: (1) The mechanical distension of the alimentary canal; (2) the presence of the pancreatic juice. Bayliss and Starling consider it probable that the secretion of succus entericus is called forth by the chemical action of the pancreatic juice upon the glands in the intestinal wall. Frouin (115) reports that the intravenous injection of the succus entericus provokes an immediate and abundant secretion

of succus entericus. The active substance in this case appears not to be secretin.

According to Lombroso (224), the prime factor in the secretion of the intestinal juice is the action of chemical substances which are produced during normal digestion, and act on the nerve endings of the mucous membrane of the intestine.<sup>1</sup>

<sup>1</sup> See also on the " Mode of Action of Secretin " (Lalou, *Journal de Physiologie*, t. xiii., No. 3, May 15, 1911).

## CHAPTER IX

### THE INTERNAL SECRETION OF THE GASTRIC MUCOUS MEMBRANE AND THE NORMAL MECHANISM OF THE SECRETION OF THE GASTRIC JUICE

It has been shown by Pawlow that psychical secretion, as well as the results of a sham meal, are entirely abolished by division of both vagi, and, further, that stimulation of the peripheral end of the cut vagus (after its cardio-inhibitory fibres have been allowed to degenerate) calls forth a steady secretion of gastric juice. These experiments show conclusively that an important—probably the most important—part of the gastric secretion is determined by a nervous mechanism [Starling (352), Biedl (25)]. Grandauer (130), as a result of numerous experiments, finds that the psychic influence upon the flow of gastric juice is marked in the human subject, as Pawlow found in the dog.

On the other hand, Ducceschi (80) finds that dogs and cats whose stomachs have been severed from any nervous connections either with the central nervous system or with the semilunar ganglion, show no particular disturbances.

However important the nervous influences may be, it is probable that the nervous secretion does not account for the whole of the gastric juice obtained as the result of a meal.

The question as to the existence of some specific hormone in relation to gastric secretion analogous to secretin was put to the test by Edkins (87). This observer found that extracts made of the pyloric mucous membrane in boiling water or HCl 0.4 per cent. contains an active substance, which, on injection into the bloodvessels of an animal, leads to a secretion of gastric juice. Extracts made in cold water, peptone, glucose, or glycerin, also contain variable amounts of this substance.

Extracts of the fundus mucous membrane, however made, do not contain this substance. The inactive condition of some extracts is due to the substance being present in an undeveloped state ; boiling the substance or treating with acid will lead to the complete development. This is, however, only the case with extracts made from the pyloric or true cardiac mucous membrane, but not the fundus mucous membrane. Atropin does not diminish the reaction of an animal to this excitant. The substance is not a ferment, as boiling an extract leads to an increase rather than a diminution of its properties.

From these experiments it would seem that we are justified in concluding that the first products of digestion act on the pyloric mucous membrane, and produce in this membrane a substance which is absorbed into the blood-stream and carried to all the glands of the stomach, where it acts as a specific excitant of their secretory activity. This substance may be called the *gastric secretin*, or *gastric hormone*.

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## CHAPTER X

### THE INTERNAL SECRETION OF THE REPRODUCTIVE ORGANS

#### A. The Internal Secretion of the Testis.

BROWN-SÉQUARD (39, 40, 41) found that subcutaneous injections of extracts of testis exercised considerable influence upon the general health, as well as the muscular power and mental activity. The experiments were performed upon himself when he was seventy-two years of age, and he describes very marked rejuvenating effects. It is probable that a good deal of Brown-Séquard's personal benefit under this treatment is to be attributed to suggestion.

More recently Poehl (292) asserts that he has prepared a substance, *spermin*, to which he assigns the formula  $C_5H_{14}N_2$ , which has a very beneficial effect upon the metabolism of the body. He believes that this spermin is the substance which gives to the testicular extracts prepared by Brown-Séquard their stimulating effect. He claims for this substance an extraordinary action as a physiological tonic. It is recommended that testicular preparations be employed in cases of deficiency of testicular substance, or in old age, when the testes lose their functional capacity. Zoth (408), and also Pregel (302) seem to have obtained definite proof by means of ergographic records, of the stimulating action of the testicular extracts upon the muscle-nerve apparatus in man. They find that injection of such extracts not only causes an increase in the amount of muscular work which can be accomplished, but lessens the subjective fatigue sensations.

The chemical composition and physiological action of Poehl's spermin and other orchitic extracts have also been investigated by Dixon (76). He finds that the preparations contain a very large amount of nucleo-protein and other



proteins, some organic substances unaltered by boiling, and inorganic salts. Injection into the circulation caused a fall of blood-pressure, but this we now know is an action common to all tissue extracts. Walker (386) is doubtful of the efficacy of testicular medication, stating that the injection of fluid extract into castrated dogs had no effect in arresting the atrophy of the prostate gland. Marshall (240), however, suggests the possibility that the "active principle" of the testicular secretion was destroyed in the preparation of the extract, and that the constant administration of fresh testicular substance might have led to a different result.

It is exceedingly doubtful how far the effects of subcutaneous injection of orchitic extracts are to be regarded as specific. Fresh (unboiled) extracts of various organs and tissues of the body have a distinct stimulating effect when administered subcutaneously to dogs, cats, and other laboratory animals.

There are, however, reasons of quite another kind for thinking that the testis pours into the blood-stream certain materials which are essential for the proper development of the body and the maintenance of normal health and vigour. The condition of persons or animals in whom the testes have not descended, or from whom the testes have been removed, is strong evidence that, besides the function of the preparation of the specific reproductive elements, the organs have other important duties to perform. There seems to be no doubt that the secondary sexual characters in the male are due to an internal secretion on the part of the testis. Castration before the age of puberty in man is well known to prevent the growth of hair on the face, to arrest the growth of the thorax, and pelvis, and the larynx (and so preserve the voice of childhood). There is in many eunuchs a tendency to a certain form of gigantism, and the mental characteristics are peculiar.

The first result of castration before the age of puberty is the hindrance to further development of the reproductive apparatus. The vesiculæ seminales and the prostate are small and atrophied. The penis does not share in the atrophy, so that in Eastern countries it is frequently considered necessary to remove this as well as the testes.

The atrophy of the vesiculæ seminales and the prostate after castration can also be noted experimentally in animals ; and, further, if castration be performed in quite young animals, the operation prevents the development of the prostate, whereas division of the vas and the abolition of the production of semen have no arresting influence [Steinach (356), Griffiths (132, 133), Wallace (389)]. The atrophy of the prostate after castration has led to the introduction of this operation as a method of treating prostatic enlargement [Ramm, cited by Biedl (25)]. Castration on one side produces no effect, the retention of a single testis being sufficient to maintain the functional integrity of both prostates. It is stated, also, that Cowper's glands atrophy after castration [Schneidemühl (330) ; see however, Nagel (260)]. It is generally assumed that the growth and integrity of the prostate are determined by a hormone furnished by the testis. On this hypothesis we might explain hypertrophy of the prostate as due to a hypersecretion of the hormone. This would not be inconceivable if we make the further hypothesis that the internal secretion proceeds from the interstitial cells of the testis, and these might still be active, or even of increased activity at a time when the seminiferous tubules are in process of degeneration.

So much for the influence exerted by the testis, in all probability by means of an internal secretion, upon the growth and development of the other generative organs. We have now to consider the influence of the testis in developing and maintaining the secondary sexual characters. It is, perhaps, well to point out that castration never induces a condition in any respects resembling the female type ; the condition is infantile, and not female. The effects in man are well known, and have already been briefly referred to. The relation between testis and secondary sexual characters is, however, closer in those animals in which we find increased testicular activity in the breeding season associated with a periodic development of other sexual characters. An example is given by Marshall (240). In the male elephant the glands on the side of the face emit a musky secretion during rut. Some interesting particulars in regard to the effects of castration upon the secondary

sexual characters are also given by Marshall, the observations being collected from Darwin (67), Cunningham (63, 64) Hegar (158), Selheim (338), and others.

If the testes are extirpated from quite young stags, the antlers never develop; if the operation is performed at the period when the antlers have just begun to grow, these remain covered by skin, forming the "peruke" antlers. If castration be carried out after complete development of the antlers, these are shed prematurely, and replaced by imperfect structures. Analogous results are recorded in the fallow deer and prong-buck (*Antilocapra americana*). As pointed out by Marshall, it is of interest to note that in the eland and in horned cattle, where both sexes possess horns, the growth and development of these structures are not affected by castration.

Changes in the bodily conformation as a result of castration in quite young animals also occur in sheep, guinea-pigs, oxen, and other animals. In the case of the cock, it is well known that castration arrests the development of the comb and spurs.

Experiments of a somewhat different nature must now be referred to. Bouin and Ancel (30) tied the vasa deferentia in different animals. The result of this operation was that the seminiferous tubules atrophied, while the interstitial cells were unaffected. These authors were the first to point out the distinctly glandular appearance of these interstitial cells. They suggest that it is owing to the presence of the interstitial tissue that the secondary sexual characters become developed, and that this is due to the activity of a definite internal secretion on the part of the interstitial cells. Bouin and Ancel report further (32) that subcutaneous injection of extract of the interstitial tissue in guinea-pigs diminishes the effects of castration, and tends to promote growth (33). In a still further communication (31), these authors state that the development of the interstitial glandular-looking tissue coincides with the first occurrence of spermatogenesis. Other authors [Lécaillon (202)] also lay great stress upon the importance of the interstitial cells of the testis.

Shattock and Seligmann (340, 341) have also studied the effect of the occlusion of the vasa deferentia in sheep and

fowl, and find that this does not hinder the full development of the secondary male characters. Since castration does hinder this development, it follows that the metabolic results arising from the functions of the testis must be attributed to the elaboration of an internal secretion and its absorption into the general circulation. These authors agree with Bouin and Ancel that the interstitial cells of the stroma have characters so unmistakably glandular that some secreting function must be assigned to them, and they may possibly be responsible for the internal secretion just referred to.

There is an important difference in the result obtained when the whole cord is ligatured from that obtained when the vas only is tied. In the former case all sexual activity comes to an end ; in the latter, after a short interval of time, the animal remains just in the same condition as the control, although, of course, reproduction is impossible in both cases. After ligature of the vas the interstitial cells remain unaltered, although the spermatogenic tissue degenerates. These results, pointing distinctly to an internal secretion on the part of the interstitial cells of the testis, have been furnished to me by Dr. Copeman. His results are generally in agreement with those of Bouin and Ancel.

Foges (107) in 1899 could not be sure that transplantation of the testis had any influence on the secondary sexual characters. In a later paper (108) he states a different conclusion. The experiment he performed was to remove the testes of fowls and transplant them to abnormal positions in the body cavity. In these later experiments—at any rate, in those which were successful, the transplanted testes had a similar influence upon the development of the secondary sexual characters to that of the normally placed testes, and the comb and spurs were developed just as in uncastrated cocks. From these experiments Foges draws the conclusion that the testes are organs furnishing an internal secretion which controls the development of the male characters.

Shattock and Seligmann have also performed some experiments upon testicular transplantation in fowls. They report that the secondary sexual characters develop to a varying extent, which seem<sup>d</sup> to depend on the amount of testicular substance left behind.

Loewy (219) and Walker (C. E.) (388) describe the results of experiments in which the development of male characters followed the injection of extracts of testis. In Walker's experiments the injections were made into hens, and the combs and wattles grew in size, and became more brightly coloured. These experiments require confirmation.

According to Marshall (240), on the authority of Corner (62) and Eccles (86), an imperfectly descended testicle in man is still of the greatest value to its possessor in virtue of its influence over the metabolism.

Very important indeed, as bearing on the question of the internal secretion of the testes, are the experiments of Nussbaum (262). At the approach of the breeding season there is formed in the male frog a thickened pad of skin on the first digit of each fore-limb, associated with an increased muscular development in the forearm. This modification is preparatory to the act of copulation, when the male frog uses its arms in embracing the female, and so assists in pressing out the eggs from the oviduct [Marshall (240)]. If the male frog be castrated, the pad is not formed, and the muscles do not develop. Nussbaum found that when pieces of testis were introduced into the dorsal lymph sac of a castrated frog, the swelling on the thumb and hypertrophy of the muscles of the leg took place just as though the frog had not been castrated. This development of a secondary sexual characteristic must have been due to the absorption of substances (internal secretions) derived from the testicular tissue, since there was no nervous connection. If, however, the nerves supplying the muscle of the forearm were severed (in an entire frog) the enlargement did not occur. A similar result was brought about on transecting the nerve supplying the glands and papillæ of the thumb-swelling. Nussbaum concludes, therefore, that the internal secretion provided by the testis acts through the medium of the trophic nerves. Pfüger (282), however, controverts this latter conclusion of Nussbaum, pointing out that in similar cases it has been shown that the apparent effect of the transection of nerves is due to the loss of sensibility in the parts concerned, in consequence of which the tissues are not guarded from injury.

Transplantation of the testis was carried out by Hunter

and by Berthold (22), and, apparently, with complete success. In cocks Berthold found that the secondary sexual characters were retained after transplantation, and the author puts forward what is practically the modern view of internal secretion, except that he considers the nervous system to play an important part.

But Rud. Wagner (385), Göbell (128), Herlitzka (166), and Foà (104, 105), were unsuccessful. Herlitzka found that the testis of Triton transplanted into the peritoneal cavity is absorbed completely, and replaced by connective tissue. Foà, also, working with mammals, records degeneration of the testis after the operation. Lode (218) and Hanau (154) are among those who have been successful.

A subject of peculiar interest is the influence of the testis upon growth in general, and upon the growth of bone in particular. There has long been a belief in a definite antagonism between growth and sexual activity. It was laid down as a general biological principle by Carpenter, Spencer, and others, that the functions of nutrition and reproduction are essentially opposed to one another, because reproduction makes such a demand upon the parent for material that the supply for nutrition and growth of the parent is lessened. This philosophical generalization has been vigorously combated by Minot (252), Morgan (256), and others. However this may be, abundant evidence has now been accumulated that the absence of the functional testis brings about abnormal growth of bony tissues. But this, according to modern views, is not due to the fact that the testis is not acting as an organ of reproduction, but to the fact that the normal internal secretion from the organ is not available for the controlling of the growth of bone in the body.

Poncet (293) in 1897 reported a series of experiments upon rabbits, in which he found that castration has a very definite effect upon the development of the skeleton. The bones of the castrated animals were stronger, but especially longer, than those of the controls. The increase in length was particularly noticeable in the femur, the tibia, and the fibula. The whole skeleton of the castrated rabbit was, however, somewhat larger than that of the control. The fact that the presence of a functional testis is inimical to bone growth

is also emphasized by Lortet (228, 229), and by Pirsche (289). The work of Pirsche firmly established the fact that castration in youth is followed by abnormal growth of the long bones. A full account of the subject, with additional details, is given by Launois and Roy (200),<sup>1</sup> and Geddes (119) has recently reinvestigated several points in connection with the matter. He reports that males whose testicles are functionless are found to possess unduly long limbs. This undue length affects the radius and tibia more than the humerus and the femur. The process of ossification is unduly prolonged. He finds, also, that in animals which have been castrated there is an increase in the length and weight of the bones, and a delay in the obliteration of the epiphysial cartilages. In eunuchs there is delay in the completion of the process of endochondral ossification. Further, the long bones of the appendicular skeleton are unduly long. This excess of length is particularly remarkable in the more distal segments of the limbs. The bones are thin, smooth, and slender.<sup>2</sup> Geddes is inclined to look upon these results as occasioned by the setting free for general use of foodstuffs which would otherwise have been used to provide for the drain of spermatogenesis. In other words, the activity of the sexual glands is opposed to body-growth. Apparently there are no experiments to determine whether simple vasotomy or ligature of the cord itself will induce these bony changes. If simply abolishing the spermatogenesis will bring about these changes, it is obvious that the theory of internal secretion would have to be abandoned.<sup>3</sup>

Loisel (220, 221) believes that one of the functions of the internal secretion of the testis is to destroy fat in the body. For this reason men are thinner than women, and castrated men become fat.<sup>4</sup>

<sup>1</sup> Launois and Roy discuss the part played by the internally secreting glands in general (thyroid, thymus, pituitary, and genital glands) in the formation of giants. They conclude that the products of their elaboration, though still unknown, are just as important for the organism as a whole as those of the glands with an external secretion. Their function is, among other things, to direct through the agency of the nervous system, the state of nutrition of certain tissues, more particularly those of mesodermal origin, connective tissue, cartilage, and bone.

<sup>2</sup> See also Pittard (291).

<sup>3</sup> See also Duckworth (81).

<sup>4</sup> Cunningham (63) gives a very interesting account of the secondary sex characters in different animals, and of the hormone theory of their develop-

### **B. The Internal Secretion of the Prostate Gland.**

Serralach and Parès (339) report that after prostatectomy in dogs the testicles gradually lose their functional activity, ejaculation ceases to occur, the formation of spermatozoa is stopped, and the other generative secretions are no longer formed. On the other hand, the administration of glycerin extract of prostate to dogs so operated upon prevents the atrophic changes; ejaculation continues, the spermatozoa do not disappear, the preputial glands secrete. It is inferred, therefore, that the functional activity of the testis and other generative organs is dependent upon an internal prostatic secretion.

Walker (387) had previously obtained contrary results with white mice. As Marshall (240) very justly points out, the most obvious criticism of Serralach and Parès' view is that it is unlikely on phylogenetic grounds, that the functional activity of the essential organ of reproduction should depend on the presence of an accessory gland of comparatively recent evolutionary development. Further, Dr. Halpenny, working in my laboratory, has repeated the experiment of Serralach and Parès upon dogs. In these there was certainly no appreciable effect upon the testes.

### **C. The Internal Secretion of the Ovary and the Corpus Luteum.**

Our knowledge of the effects of extirpation of the ovaries before the age of puberty in the human subject is very limited. A fairly large number of operations must have

ment. He has further made an attempt to apply the hormone theory to the subject of heredity. He argues that, since the development of the somatic sex characters is due to the stimulation of the cells by a hormone derived from the gonad, it is conceivable that the gametes may be affected by the internal secretion of the somatic cells, whose development constitutes the sex character. For example, a somatic sexual structure, such as the antler of a deer, would secrete special substances into the blood, and the gametes would be multiplied and developed under their influence.

It will have been gathered from what has been said previously, that in the opinion of the present writer such a theory is carrying the idea of internal secretion far beyond the limits which should be laid down by our present knowledge. Such structures as antlers do not, so far as we know, furnish an internal secretion (see p. 12). The view of Cunningham is based upon the theory mostly held by French writers, that all tissues and organs furnish a specific internal secretion. This matter has been discussed in Chapter II.

On this subject of hormones and heredity, see also Bourne (34, 35).



been performed in which female children were deprived of both ovaries at an early age, but there seems to be no systematic account of them. Marshall (240) states that such extirpation, besides preventing the onset of puberty and the occurrence of menstruation, produces noticeable effects on the general form and appearance. He instances the case of certain adult women in semi-barbarous parts of Asia, where the natives perform this operation upon young girls. Such women are said to be devoid of many of the characteristics of their sex, and in certain cases to present resemblances to men. This account seems to be derived from the observations of Robert in the East Indies. According to Biedl (25), however, there is no ovariectomy among such people, but simply mutilation of the external organs of generation. Indeed, it seems incredible that savages could perform double ovariectomy.

When extirpation of both ovaries is carried out in the human female after the age of puberty, the most marked effect is the cessation of pregnancy. There is also in some cases an atrophy of the breasts, uterus, vagina, and external genitals. A tendency to obesity is also recorded.

In some female animals removal of the ovary has been stated to lead to the appearance of male characters. Cases are recorded in which female deer possessed horns. In these the ovaries were abnormal or the animals were old. Similar cases are not uncommon in birds.<sup>1</sup> Such cases are difficult to explain on any other hypothesis than that the secondary male characters are normally present in a latent form in the female, and that the ovaries exert an inhibitory influence over their development. As we have seen above (p. 69), castration in the male never induces a condition in any respects resembling the female type.

All the foregoing facts show that the ovary, just like the testis, has a far-reaching influence over metabolism. Until recently this influence has generally been supposed to be nervous. As we shall see in the succeeding paragraphs, the evidence as to some kind of internal secretion is now tolerably conclusive.

Knauer (179-183) has shown that removal of the ovaries

<sup>1</sup> Numerous cases are quoted by Marshall (240) on the authority of Darwin, Hunter, and others.

prevents the occurrence of the oestrous cycle, but that if ovarian tissue be grafted into the muscles of the animal, the "periods" begin again. Knauer found, however, that some portion of the grafted ovary always degenerated, while a part produced ova which could be fertilized. This author further found that castration caused atrophy of the uterus, and this could be prevented by successful transplantation of ovary. The experiments were performed upon dogs and rabbits. The results were confirmed by Grigorieff (134), Ribbert (311), and Rubinstein (316),<sup>1</sup> and similar results were obtained by Halban (141, 142) and by Limon (214).<sup>2</sup>

During the last six or seven years a considerable amount of work has been done upon the structure and functions of the corpus luteum. This body in its fully formed state consists of columns of large cells (luteal cells), containing a yellowish pigment. The columns are separated by intervening trabeculae, composed of fibrous tissue containing numerous bloodvessels. These trabeculae converge inwards from the surrounding ovarian stroma to a central strand or plug of connective tissue, in which there are no luteal cells, occupying the axis of the nodule (see Fig. 13). The columns of cells are not unlike those of the cortex of the adrenal (see Figs. 13 and 14). The fully developed corpus luteum is a highly vascular structure.

The fullest and most complete account both of the development and of the histology of the fully formed corpus luteum is given by Sobotta (344, 345, 346). In the mouse (345) the epithelial cells are large and polygonal in shape, measuring 20  $\mu$  or more in diameter. The cells contain fat, which is mostly disposed excentrically, but it may almost fill the entire cell. The peripheral cells are for the most part free from fat, while those in the centre contain the largest amount. Generally speaking, the older a corpus luteum is the more fat does it contain. The nucleus is rounded. The connective tissue is in the form of spindle-shaped anastomosing cells. They surround groups of four to five epithelial cells by anastomoses of their processes. Their nuclei closely resemble those of the capillary walls.

<sup>1</sup> See also Sokotoff (348).

<sup>2</sup> Other papers on ovarian transplantation are those of Carmichael (51) Herlitzka (167), Foà (103), Schultz (335).

The connective tissue of the central plug consists of stellate elements. In some animals the fully formed luteal cells are rounded or spindle-shaped, and may show signs of degeneration.

The mode of formation of the corpus luteum is still under discussion. Former investigators were not able to agree as

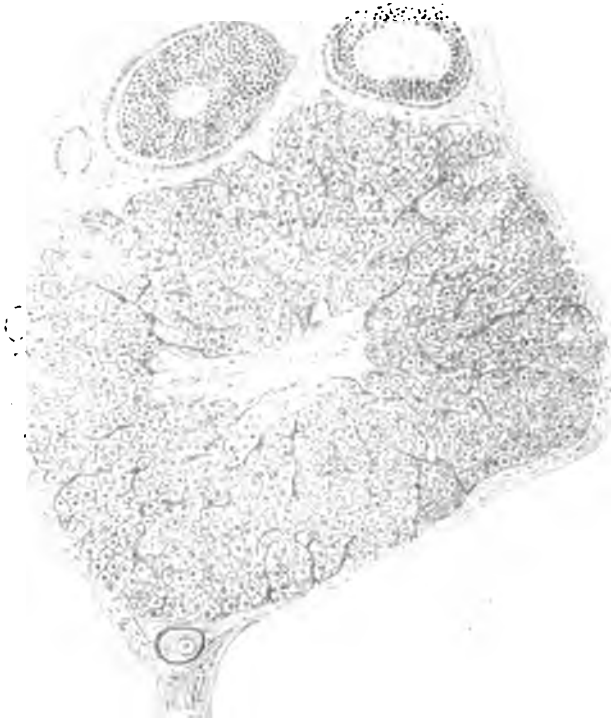


FIG. 13.—Section through the ovary of *Dasyurus viverrinus*, showing Graafian follicles and corpus luteum. (Drawn by Mrs. F. D. Thompson from material supplied by Mr. Charles O'Donoghue.)

to whether the body is a connective-tissue structure, or whether the luteal cells are formed by the hypertrophy of the epithelial cells of the undischarged Graafian follicle. The former theory is that of v. Baer (11), the latter that of Bischoff (27). The investigations of Sobotta (344, 345, 346) upon the mouse and the guinea-pig confirm Bischoff's view, but there have been several investigators who could

not adopt this theory. There is no need to enumerate the authors who have held one or the other view on this question. An admirable account of the history of the controversy is given by Marshall (240) and by Clark (57, 58). There is a tendency towards a compromise in some of the recent papers. Thus, van der Stricht (357, 358) found that, whereas the majority of the luteal cells are derived from the follicular epithelium, a certain number are developed out of interstitial cells in the inner theca of the connective-tissue sheath. As pointed out by Marshall (240), this is of special interest in view of the statement made by Miss Lane-Clayton (198) that the follicle and interstitial cells have an identical origin, since both are derived from the germinal epithelium, and pass through a similar series of changes. The majority of recent investigators are, however, in favour of the view that the luteal cells are derived from the follicular cells.

The glandular nature of the organ is admirably shown in the corpus luteum of *Dasyurus* (see Figs. 13 and 14).

The idea that the corpus luteum might be an organ with an internal secretion was first conceived by Gustav Born, who suggested that the function of the internal secretion was to subserve the fixation and development of the impregnated ovum in the uterus. Born did not publish his views, but bequeathed the idea to Fraenkel to work out. This author (112, 113) believes that not only does the corpus luteum minister to the special needs of the gravid uterus, but that upon its secretory activity depends also the occurrence of the œstrous cycle. The arguments put forward are not entirely satisfactory, and it is not easy to see how this author would explain the occurrence of the first œstrus in young animals (Marshall, 238).

The theory that the corpus luteum is a gland with an internal secretion has also been brought forward by Prenant (303). This writer points out that its morphological and histological characters are those of a glandular apparatus without a duct, and that the cells of the corpus luteum elaborate material in their interior, as has recently been more fully described by Regaud and Policard (307, 308). Prenant believes that the purpose of the corpus luteum is probably to prevent ovulation in the period between successive œstrous

periods or during pregnancy. This theory is supported by Sandes (321), who worked at the formation of the corpus luteum in *Dasyurus*. Why it should be necessary for an animal to elaborate an organ having this function does not seem clear, especially in view of the fact stated by Sandes, that the ova degenerate in the ovary, and are not preserved for succeeding ovulations.

Some years ago, in conjunction with Dr. F. H. A. Marshall, the present writer performed a series of experiments designed

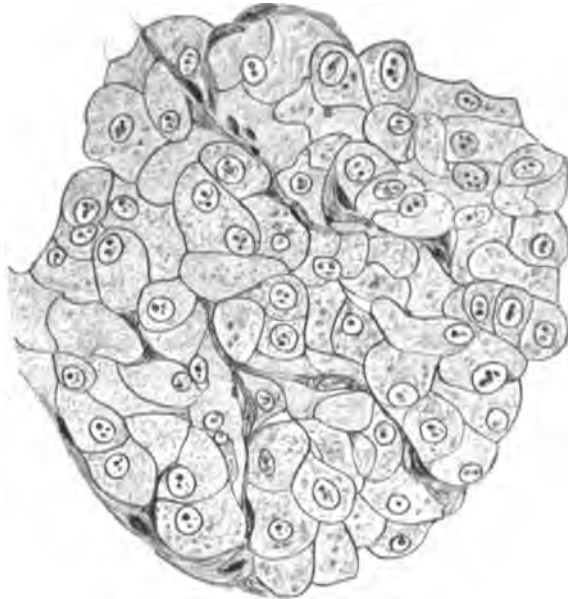


FIG. 14.—Portion of corpus luteum of *Dasyurus* under a high power, showing the glandular nature of the constituent cells. (Drawn by Mrs. F. D. Thompson from material supplied by Mr. Charles O'Donoghue.)

to test the theory that the œstrous cycle is determined by an internal secretion on the part of the ovary. We made extracts from ovaries in a pro-œstrous or œstrous condition, and injected them subcutaneously into a bitch at a period as remote as possible from the œstrous one. In some of these experiments a swelling of the vulva and other slight signs of the œstrous condition were induced, but the results were not decisive enough to warrant us in publishing them. The departure for Canada of the present writer put an end

to this series of experiments. Since then, however, Marshall and Jolly (243) report that "heat" or a transient condition resembling it can be produced by the injection of extracts of oestrous ovaries, and, further, that when oestrous or pro-oestrous ovaries are successfully grafted into an animal previously deprived of its ovaries, the condition produced is identical with a normal heat, and that irrespective of the situation of the graft. Marshall and Jolly consider that the ovary is an organ providing an internal secretion which is elaborated by the follicular epithelial cells, or by the interstitial cells of the stroma. This secretion circulating in the blood induces menstruation and heat. After ovulation, which takes place during oestrus, the corpus luteum is formed, and this organ provides a further secretion, whose function is essential for the changes taking place during the attachment and development of the embryo in the first stages of pregnancy. This result is in general agreement with that part of Fraenkel's theory which assigns to the corpus luteum the function of governing the fixation of the ovum. Whether this conclusion is correct or not there can be little doubt that the growth of the corpus luteum during early pregnancy is functionally correlated with the hypertrophy and congestion of the uterus.

"Heat" in animals cannot be induced by an internal secretion arising in the corpus luteum (as supposed by Fraenkel), since ovulation in dogs and probably most mammals normally takes place during oestrus, and consequently there are no corpora lutea (or, at any rate, no fully formed corpora lutea) present in the ovaries during the pro-oestrus—*i.e.*, during the stages of uterine hypertrophy and congestion, and the subsequent degeneration which characterizes this period. It is concluded, therefore, that "heat" is probably brought about by an internal secretion of the ovary, and not of the corpus luteum [Marshall and Jolly (243)].

Mulon (259) has recently expressed views entirely in accordance with those of Marshall and Jolly.

As a result of a statistical investigation upon fertility in Scottish sheep, Marshall (239) has shown that a system of treatment whereby the sheep received additional or artificial food—*e.g.*, maize cake or dried grains—for a few weeks

prior to the usual breeding season, not only materially increased the fertility, but also had the effect of hastening the breeding season, and bringing the sheep "on heat" sooner. It was concluded, therefore, that the special feeding exercised a stimulating influence upon the secretory function of the ovaries.

A series of experiments upon castration and ovarian transplantation in rats [Marshall and Jolly (241)] yielded the conclusion that the existence of ovarian tissue is an essential factor in normal uterine nutrition, and, further, that the nature of the ovarian influence upon the uterus is chemical rather than nervous, since the successfully transplanted ovaries, while still maintaining their functions, had lost their normal nervous connections. It was rendered extremely probable, therefore, that the uterus is dependent for its proper nutrition upon substances secreted by the ovaries, not only at the heat periods and during pregnancy, when they show their greatest activity, but throughout the whole of the oestrous cycle. The ovaries were usually transplanted on to the peritoneum, where they underwent the same cyclical changes as normal ovaries, ovulating in the breeding season, and giving rise to corpora lutea. Transplantation into other individuals (heteroplastic transplantation) was more difficult to perform successfully than homoplastic transplantation. After simple removal of the ovaries for six months the uterus was found to have undergone considerable fibrosis in the mucosa and atrophy in the muscular layers; the uterine glands also degenerated. After homoplastic transplantation to the peritoneum for six months, on the other hand, the uterus was normal. Uterine atrophy was also arrested by a successful heteroplastic graft.

Carmichael and Marshall (52) have found in a series of experiments upon rabbits that complete removal of the uterus from very young animals did not arrest the further growth and development of the ovaries. Such rabbits, after growing up and becoming mature, experienced normal oestrus, copulated, and ovulated, and formed corpora lutea. On the other hand, in control rabbits belonging to the same litter, whose ovaries were removed, the uterus remained infantile, although the animals reached the normal size. Furthermore, complete hysterectomy in rats did not tend

to ovarian degeneration, since the ovaries, six months or more after the operation, were absolutely normal. These experiments, therefore, lend no support to the theory advanced by Zweifel (410) and others, that the ovaries are dependent for their functional activity upon a secretion elaborated by the uterus.

Ovaries of rats have been transplanted on to the peritoneum or into the kidneys, either of the same or of other rats [Marshall and Jolly (242)]. Homoplastic transplantation was found to be successful after fourteen months' grafting, and heteroplastic after six months. In another experiment the ovaries were removed from a monkey, and grafted on to the peritoneum of another monkey (heteroplastic transplantation). At the same time the ovaries of the latter were removed from the normal position, and also grafted on to the peritoneum (homoplastic transplantation). About two months later the monkey with the grafted ovaries was killed, when it was found that the heteroplastic ovaries had been absorbed, while the homoplastic ovaries were still in position, but had undergone a certain amount of fibrous degeneration. As a result of the experiments upon rats, the following conclusions may be drawn :

1. Greater success attends transplantation of the ovaries into the kidney than on to the peritoneum, probably on account of the greater vascularity of the kidney.

2. Homoplastic transplantation of ovaries is very considerably easier to perform successfully than heteroplastic transplantation. This fact can scarcely be ascribed to differences in the technique of the two operations, since this was identical in each experiment, the two animals being operated upon simultaneously in the case of the heteroplastic transplantations.

3. Heteroplastic transplantation of ovaries is apparently easier to perform successfully when the two animals employed in each experiment are near relatives of each other. In the experiments of Marshall and Jolly there were few exceptions to this rule.

4. The presence of an animal's own ovaries does not seem to exert any inhibitory influence on the successful attachment and growth of additional ovaries obtained from another individual.



5. The presence of a successfully grafted ovary in an abnormal position in the body, whether obtained from the same or from another individual, is sufficient to arrest the degenerative changes which habitually take place in the uterus after the complete extirpation of the ovaries, as other experiments have shown. It may be concluded, therefore, that the ovarian influence on the uterus is chemical rather than nervous in nature.

Working with rabbits, Carmichael and Marshall (53) showed that one-sided oöphorectomy may be followed by compensatory hypertrophy on the part of the remaining ovary, which in some cases weighed twice as much as the ovary previously removed. The differences between the weights of the two ovaries in each experiment had little or no relation to the periods of the year at which the ovaries were respectively removed, for the rabbits killed during the non-breeding season (when the ovaries had no corpora lutea) afforded as much evidence of compensatory hypertrophy as those killed during the usual breeding season.

Daels (65) removed the ovaries in guinea-pigs and rats. Bilateral removal always interrupted pregnancy, if performed during the first half of its duration. Control operations, in which portions of parametrium and mesentery, or one ovary, were removed, did not interrupt pregnancy. These experiments, therefore, confirm the views of Fraenkel and of Marshall and Jolly.

Flatau (95) records a number of cases in the human subject in which ovariectomy did not interrupt pregnancy, but hardly any of these were in early stages, and it is to be noted also that there was no post-mortem evidence of *complete* removal of the ovaries.<sup>1</sup>

Foges (109) came to the conclusion that the ovary is by its internal secretion necessary for the development of the mammary gland, but not for the secretion of milk. Rather does the *absence* of ovarian function (in the view of Foges) increase the secretion of milk. A good deal of evidence has

<sup>1</sup> References to other papers previous to those of Marshall and Jolly are given by these authors (242). Recently Carrel and Guthrie (54, 137, 138) have adopted a new method for the heteroplasmic transplantation of the ovary, which appears to be completely successful. The experiments, however, have little bearing on the subject of internal secretion, for there is no change in the position of the ovaries, and the normal functions are not interrupted.

been accumulated to show that the stimulus to the growth of the mammary glands arises in the ovary. The suggestion of Lane-Clayton and Starling (199, 351) that the foetus furnishes the hormone which causes growth of the mammary glands, and the criticisms of Heape (157), have already been referred to (pp. 16 and 24). In view of some recent investigations, it seems exceedingly probable that it is to the corpus luteum that we must look for the origin of the mammary hormone. O'Donoghue (263), working upon the growth of the mammary gland in *Dasyurus*, has found that the enlargement of the mamma commences quite apart from fertilization, and is continued when there is no fertilized ovum present to produce an internal secretion. This author gives tables and curves to show that as soon as the corpus luteum has begun to be formed, the growth of the mammary gland commences, and this growth is notably increased after the corpus luteum is fully formed. "These considerations render it probable that at any rate in *Dasyurus* we may regard the corpus luteum as a ductless gland producing an internal secretion which, in addition to its other functions, is intimately connected with, if not, indeed, the actual inciting cause of the growth of the mammary gland" [O'Donoghue (263)].

It is interesting to note that Ancel and Bouin (8) have shown that, in the rabbit, when the appearance of the corpus luteum followed coition with a male, part of whose vasa deferentia had been ligatured for some months, or the artificial rupture of the follicle, there was a large growth of the mammary glands. This growth was very noticeable by the fourth day, and continued up to the fourteenth day, after which regression set in. It would be interesting to test the matter further by the employment of extracts of corpora lutea, as this experiment does not seem to have been performed successfully by any of the workers upon the subject.

It is clear, as O'Donoghue points out, that the growth of the mammary glands during the last half of pregnancy cannot be due to the corpora lutea, for they have disappeared. It is possible, as O'Donoghue suggests, that the growth after this time is largely due to an increase in the size of the individual cells and a distension of alveoli and ducts.

From the foregoing description of experiments and enunciation of hypotheses, we may perhaps justly summarize, as regards the ovary, somewhat as follows: The ovary, in addition to its function of the formation of the ova, is an organ furnishing an internal secretion or secretions, which affect the general metabolism of the body and control the nutrition of the uterus. The secretion determines the processes of the œstrous cycle, and the general condition of the female organs of generation and the mammary glands. The corpus luteum is an essential factor in maintaining the raised nutrition of the uterus during the earlier stages of the period of gestation, and so helps in the fixation of the embryo. The corpus luteum also determines by a specific internal secretion the increased growth of the mammary glands after ovulation or impregnation.<sup>1</sup>

#### D. Ovarian Medication.

Brown-Séquard (40), in his first communication to the Société de Biologie, in June, 1889, expressed the opinion that the ovaries of animals might furnish a juice which would have a beneficial effect upon women similar to that obtained in the case of men by the employment of testicular extracts. In 1890 (42) he reports that a Parisian midwife had injected herself with a liquid made from the ovaries of guinea-pigs, and had benefited thereby. He further calls attention to a report of Villeneuve (373), who made injections of ovarian extract into three individuals—two women and one man. One of the women, who had undergone double ovariectomy, was very considerably benefited. Finally, he gives an account of the work of an American lady doctor, Mme. Augusta Brown, who “avec un grand courage” had observed good results by injection of extracts made from the ovaries of rabbits. The injections were mostly subcutaneous, but the application was sometimes made on to the skin after blistering, and in one case the juice was applied directly to the uterus (in the case of prolapse).

Brown-Séquard does not seem to regard these reports as of much value, for he concludes that it is the testicular juice which ought always to be given “comme agent dynamo-

<sup>1</sup> For more recent accounts of ovarian grafts see Sauvé (322) and Tuffier and Chapman (369).

génique" in women as well as in men. He states that the ovarian extracts are less powerful than the testicular, and their action is not specific.

Mainzer (231, 232) obtained good results in the treatment of heats, sweating, headache, etc., after double ovariectomy, and also in the vasomotor troubles of the menopause.

Bestion de Camboulas (23) gives a good history and many interesting references showing how completely persuaded were many physicians of the period that the ovary is a gland with an internal secretion. The evidence at their disposal was, however, very meagre. They seem to have been led to their belief chiefly by Brown-Séguard's famous dictum that all glands, whether or not they possess a duct, pour into the blood useful principles, whose absence makes itself felt after their extirpation or their destruction by disease.<sup>1</sup>

Bestion de Camboulas gives an account of the various modes of preparing ovarian extracts. He employed (1) fresh gland, (2) dried gland, (3) ovarian juice or fluid extract. This last was watery or alcoholic, or a glycerin extract. He recommended the employment for medical purposes of the ovaries of the sow.

This author performed a series of experiments upon animals in order to investigate the toxicity of the ovarian extracts, and found that the glycerin or watery preparation is much more toxic for the male than for the female. After large doses males died with pyrexia, hæmaturia, and other disturbances. With non-toxic doses the males lost weight, the females gained weight. The resistance of pregnant females was much less than that of non-pregnant.

Clinically, his results were as follows: Troubles of the menopause, natural or after castration, are considerably relieved by ovarian extract without other medication. There is constant amelioration in cases of amenorrhœa and chlorosis, and there is a real improvement in the mental troubles which accompany genital lesions, or which occur after castration. Improvement in the general condition is marked in all cases. The extract should never be given to pregnant women.

Andrews (9) speaks very cautiously as to the benefit

<sup>1</sup> Bestion de Camboulas says naively: "The ovary, being a gland, ought not to escape this law."

accruing from the administration of ovarian extracts, while Cohn (60) finds that the results are nearly always disappointing.

Batty Shaw (342) says that the special value of ovarian substance is shown in cases in which the ovaries are ill-developed, or have become atrophied as at the menopause, or have been removed by operation.

There are numerous other papers on the subject of ovarian medication. Reference to these will be found in the works of Andrews, Shaw, and Bestion de Camboulas. No good can be derived from a more detailed study of reports on ovarian medication. Much of the work has been very uncritical. No due regard has ever yet been taken even in experiments on animals as to the condition of the ovary from which the extract is made, and it seems clear that the corpus luteum will in the future have to be separately considered both experimentally and clinically.<sup>1</sup>

<sup>1</sup> Bouin and Ancel (*La Presse Médicale*, No. 55, 12 Juillet, 1911) now believe that the corpus luteum secretes a hormone which excites the mammary gland to growth, but that the hormone which excites to secretion is derived from a gland which they claim to have discovered in the muscular layer of the uterus, and to which they have given the name "myometrial gland." For a recent résumé of this and other work upon mammary secretion, see Schil, "Recherches sur la Glande Mammaire," Nancy, 1912.

## CHAPTER XI

### THE INTERNAL SECRETION OF THE ADRENAL BODIES

(The Cortex of the Adrenal and the Chromaphil Tissues)

#### A. Introductory.

WHEN we consider the extraordinarily voluminous literature devoted to the adrenal bodies, and the immense amount of time and patience which has been expended by physiologists, pathologists, and comparative anatomists, in the attempt to elucidate their function, it is regrettable to have to admit that we are still unable to give a full and satisfactory answer to the question, "What is the function of these bodies?" We have, perhaps, a fairly reasonable suggestion to offer as to the service in the economy rendered by the chromaphil tissues (including what in mammals is called the "medulla" of the adrenal), but of the physiology of the "cortex" we know practically nothing.

There are two important discoveries which stand out among all others as epoch-making. The first is the observation by Addison (27, 28, 29) 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 (537, 538, 539) 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 (688, 689) and Aldrich (35, 36, 37) independently.

An interesting account of the development of our knowledge of the adrenals up to the time of Addison (1849) is given by Biedl (104). Other accounts of the older history will be found in the works of Blanchard (114, 115), Cuvier (199), Delle Chiaje (207, 208, 209), Arren (50), Pettit (567), and Caillan (153). It will not be possible to find space for reference to more than a few of the striking historical landmarks.

The passages in the Vulgate (cap. iii., vers. 4, 9, 10, and 15 ; cap. iv., ver. 8 ; cap. v., ver. 9 ; cap. vii., ver. 4 of Leviticus) in which "renunculum" is supposed to refer to the adrenals (Delle Chiaje, 207), have been shown by Blanchard (114, 115) to be mistranslations from the original Hebrew text. There is no evidence that the adrenals were known to the ancient Hebrews, nor to the Greeks and Romans [Blanchard (114, 115) ; Biedl (104)].

The first definite account of the adrenals with illustrations is given by Eustachius (252) in 1563. For a long time the discovery was unnoticed, or the existence of the new organ was denied ! It is indeed remarkable, as pointed out by Biedl (104) that Vesalius in 1642 (719), Fallopius in 1606 (257), and Fabricius in 1738 (256) make no reference to the bodies discovered by Eustachius. However, they began to be referred to even before the end of the sixteenth century in the medical books as the "glandulæ" or the "capsulæ renales Eustachii."

The story of Montesquieu's participation in the history of our subject is so interesting that, although it has now been told several times, it will well bear repeating.

In the year 1716 the Academy of Sciences of Bordeaux offered as the subject of a prize essay, "What is the Use of the Suprarenal Glands?" The essays submitted were placed in the hands of Montesquieu, the famous author of the "Esprit des Lois," who acted as judge. His report is of especial interest, not only because of the personal fame of the author, but because it gives an admirable critical account of the older views upon the adrenal bodies. The style is satirical, but it is probable that it was not intended to be so satirical as it appears to us at this date, when every theory mentioned in 1716 appears to us positively absurd. Montesquieu briefly discusses the older views that the glands

serve to hold up the stomach and strengthen the nervous plexus which touches them, or that "black bile" is preserved within their cavity (Bartholin), or that they serve to collect the humidities which leak out of the great vessels in the neighbourhood. He then criticizes the essays which were presented to the Bordeaux Academy.

"We have found one author who declares that there are two kinds of bile : one grosser, which is separated out in the liver ; the other more subtle, secreted in the kidneys by the assistance of the ferment which flows from the suprarenal capsules by ducts of which we are ignorant, and of which," comments Montesquieu, "we are menaced with perpetual ignorance."

"Another describes to us two small canals which carry the liquids from the cavity of the capsule into the vein belonging to it ; this humour, which many experiments lead us to consider alkaline, serves to give fluidity to the blood returning from the kidneys after it has been deprived of serosity in the formation of the urine.

"Another essayist, who gives a difference between conglobate and conglomerate glands, has placed the suprarenal glands among the conglobate. In his opinion they are nothing but a continuity of bloodvessels within which, just as in filters, the blood becomes more subtle. . . . In these glands, as in all the conglobate glands, no excretory duct exists, because there is no question of the secretion of liquids, but only of making them more subtle."

In conclusion, Montesquieu announces that the Academy will not award its prize this year, since the object of the offer has not been achieved. He ventures his own opinion that "le hasard fera peut-être quelque jour ce que tous ses soins n'ont pu faire," and he is polite enough to state : "Mais ces efforts impuissants sont plutôt une preuve de l'obscurité de la matière que de la stérilité de ceux qui l'ont traitée."<sup>1</sup>

In attempting to assign a function to the adrenal bodies, it is essential to constantly bear in mind their dual nature. As we shall see later, the adrenal body of the higher vertebrates has been derived from two separate and distinct kinds of tissue in lower vertebrates ; and although there is a more or less gradually increasing tendency for the two

<sup>1</sup> The above account is largely taken from Biedl (104).



tissues to become united as we ascend the scale, yet it is only in mammals that the "adrenal cortex" and "adrenal medulla" are strictly appropriate.

It is absolutely essential that, before dealing with the physiology of the adrenals, we should give some account of the comparative anatomy and development of the organs.

## B. Comparative Anatomy of the Adrenal Bodies.<sup>1</sup>

### 1. *Introductory.*

It is only in the Amniota that we find a definite organ whose parenchyma is divided into two distinct portions, whose cellular constituents are quite different in character from each other.

In the Anamnia we have the organ represented by a number of small bodies. The Amphibians in some respects occupy an intermediate position. In Pisces and Cyclostomata we find two distinct categories of bodies each consisting of a special form of cell, which categories are homologous with the two constituents of the adrenals of higher vertebrates.

In Amphioxus nothing corresponding to the adrenals has so far been discovered, and in the Invertebrata the matter may perhaps be considered doubtful.

### 2. *Invertebrata.*

Leydig (462), in a most interesting passage, discusses the possibility of the existence in some Invertebrata of the equivalents of the adrenal bodies. He says: "Es sind in verschiedenen Wirbellosen am Nervensystem Zellen beobachtet worden, die von die gewöhnlichen Ganglienkugeln differierten. So habe ich schon früher von *Paludina vivipara* mitgeteilt, dass an den vegetativen Nerven eigentümliche zellen vorkommen, die vielleicht Ganglienkugeln eigener Art sind; sie sind gelblich, haben im Innern verschiedene Bläschen und stehen in keinen directen Zusammenhang mit den Nervenprimitivfasern. Auch an den Ganglien von *Pontobdella verrucosa* machten sich besondere zellen mit gelbkörnigem Inhalt auffällig." He quotes also a descrip-

<sup>1</sup> In the compilation of this section I have derived great assistance from the article by H. Poll in "Hertwig's Handbuch" (596).

tion of Meissner concerning similar cells in *Mermis*, and concludes: "Meine meinung bezüglich dieser zellen von unbekannter Bedeutung an *Paludina*, *Pontobdella*, *Mermis* (und wahrscheinlich wird ein nähres Nachsehen die Zahl der Beispiele sehr vermehren) geht dahin sie als Analoga der Nebennieren vorläufig zu betrachten."

Some years ago the present writer had considered the possibility of the existence of the representatives of cortex and medulla of the adrenal bodies in the Invertebrata, but had not succeeded in finding any organs or tissues which seemed at all likely to correspond to them. But just previously to that time physiological research had rendered it possible to test any unknown organ or tissue to see if it should be homologous with adrenal medulla. An extract made from the medulla of the adrenal or from any (chromaphil) tissue of the same nature possesses powerful blood-pressure-raising properties [Oliver and Schäfer (537, 538, 539); Swale Vincent (721, 725)].

Accordingly the nervous system was dissected out as completely as possible from about a dozen fair-sized specimens of *Paludina vivipara*. The material (in which, of course, were included the groups of cells described by Leydig) was then made into a decoction by boiling for a short time with normal saline solution, and carefully filtering. This was then injected into the venous system of a cat while a record of the blood-pressure was being taken. The result was quite negative; there was not the slightest rise of blood-pressure. Now, if these cells described by Leydig represent any part of the adrenal bodies at all, this would be the medulla, since it is the medulla which is found in Vertebrata to bear a close relationship to the nervous system. But medullary substance, or, as we should now say, chromaphil substance, when injected into the venous system of a living mammal, always causes a marked rise of blood-pressure. It was concluded, therefore, from this experiment that we are justified in dismissing these groups of cells from consideration as the physiological homologues of the adrenal medulla, and that the question of the existence of adrenals in Invertebrata must be regarded as open.

But this physiological test possibly gave negative results, because the material necessarily contained so much nervous

tissue, which is active in an opposite sense—i.e., would tend to lower the blood-pressure [Osborne and Vincent (546, 547)]. In the case of the sympathetic ganglia this has actually been found to be the case [Cleghorn (182)]. The author finds that glycerin and saline extracts of sympathetic ganglia produce a fall of blood-pressure, in spite of the presence in these ganglia of chromaphil cells like those in the medulla of the adrenal body.<sup>1</sup> It appears, also, that it is impossible to obtain any rise of blood-pressure by injecting extracts of carotid glands into an animal, because there is so much admixture with various tissues whose extracts have a depressor effect [Vincent and Sheen (732, 733)]. (See, however, below, p. 175.)

Poll and Summer (589) describe certain cells in the abdominal ganglia of *Hirudo medicinalis* which stain a yellowish-brown with Müller's fluid. They consider it probable that these are homologous to the chromaphil cells discovered by Stilling (667, 668). Such cells were later described in a large number of leeches—Gnathobdellidæ and Rhynchobdellidæ [Poll (587)]—and still later Poll gives a description and some very convincing drawings of these chromaphil cells in *Nephtys scolopendroides*. As regards the yellow cells of *Pontobdella* described by Leydig, these appear to be of a different nature. As pointed out by Poll, we are sadly in need of another micro-chemical test for adrenin-containing tissues. If the ferric-chloride reaction could be used for histological purposes, it would clear up many doubtful points.

Roaf and Nierenstein (612, 613) have expressed their belief that there is a substance in the hypobranchial gland of *Purpura lapillus* which is allied chemically and physiologically to adrenalin. But the identity of the substance with adrenalin is denied by Dubois (225). Roaf has recently returned to the subject (611), and finds that in *Purpura lapillus* there are associated (1) a pressor substance in the strip of tissue adjacent to the so-called rectal gland; (2) a purple-forming material in the same area; (3) a collection of bichromate-reacting granules also in the same situation.

<sup>1</sup> Cleghorn did not ascertain that this result might be obtained from any nervous tissue, whether brain, spinal cord, or peripheral nerve [Osborne and Vincent (546, 547)]; in fact, he states that this is not the case.

The inference is that these, if not identical, are at least functionally associated.

It is curious that, so far as I can ascertain, Poll and Roaf make no reference to each other's work. It is clear that the structures they respectively describe are quite different from one another. The tissue described by Roaf is not apparently connected with the nervous system, while the chromaphil cells of vertebrates are always intimately related to the sympathetic. The cells described by Poll are, on the other hand, within the central nervous system, and, at any rate, bear a very great resemblance to the cells which are familiar to us in the vertebrate sympathetic.

### 3. *Anamnia.*

In the Cyclostomata, the lowest vertebrates in which adrenal elements are certainly known to exist, our knowledge is confined to the Petromyzonta and Bdellostoma.

In Petromyzon [Giacomini (304)] there are two distinct series of bodies. One of these is represented by small, irregular, lobulated structures in the wall of the posterior cardinal veins and the renal arteries, and of arteries dorsal to the kidney. They project into the lumen of the vessels, and consist of cylindrical or polyhedral cells, containing granules which stain black with osmic acid. These are the cortical or inter-renal bodies. The other series, or the chromaphil series, extends from the region of the second gill cleft to the tail of the animal. The bodies of this series are thin strips of tissue running along the large arteries and their branches. These bear the same relations to the veins as the cortical bodies.<sup>1</sup>

In Bdellostoma the chromaphil cells have been observed, but not the inter-renal or cortical [Giacomini (307)].

The relationships of the two adrenal representatives in Elasmobranchs were first suggested by Balfour (64) in 1878. He called the representative of the cortex the "inter-renal," while what we now know as the "chromaphil corpuscles" (representing the medulla of the adrenals of higher verte-

<sup>1</sup> The present writer, working in conjunction with Mr. W. E. Collinge (184), made an attempt some years ago to find the adrenals in Cyclostomata, but we considered that there was no satisfactory evidence to show that the bodies described by Rathke, Müller, and others had anything to do with the adrenals. In this paper will be found an account of the early history of the subject.

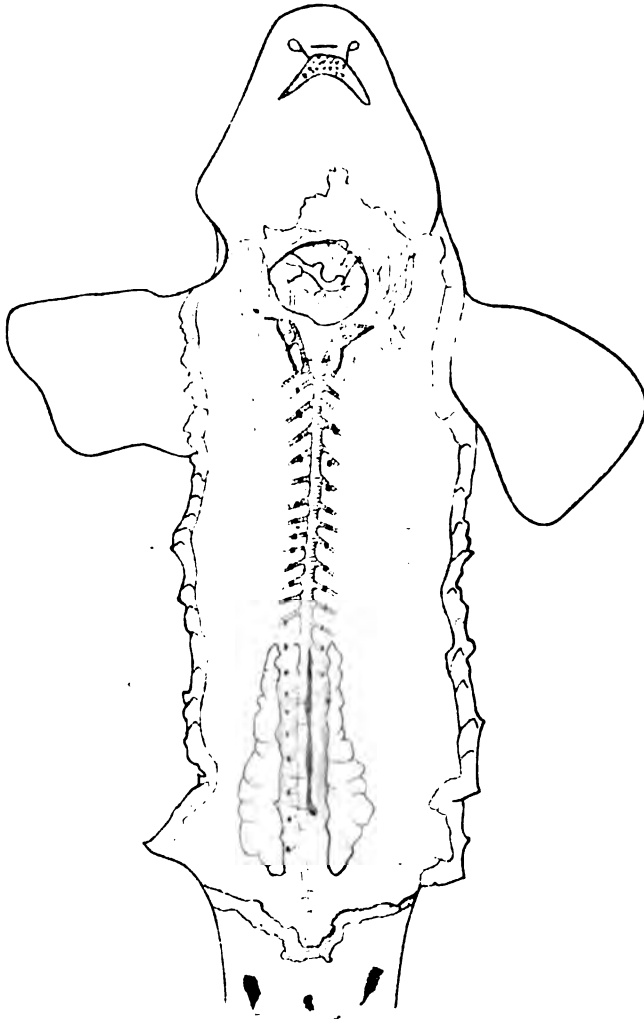


FIG. 15.—Dissection of *Scyllium canicula* (young female specimen), giving a ventral view of "paired suprarenals" (chromophil bodies) and the inter-renal (cortical body). The parovarium has been dissected away. This drawing may be taken as a typical representation of the position of these bodies in Elasmobranchs. The connections with the sympathetic are indicated to some extent in the anterior part of the figure. The chromophil "suprarenals" were displayed by Semper's chromic-acid method.

brata) he called "suprarenal bodies." That the paired "suprarenal bodies" of Balfour really correspond to the medulla of the mammalian organ was first definitely shown by the present writer (721, 725) by the physiological test. This was fully confirmed by the chemical test [Moore and Vincent (516, 517)]; and that the "inter-renal" of Balfour is really homologous with the cortex of the mammalian body was rendered clear from the negative physiological and chemical tests, and from careful histological comparisons.

The paired "suprarenal bodies" (chromaphil) are situated on branches of the aorta, segmentally arranged, and extend on each side of the vertebral column from the front part of the sinus of Monro to the posterior end of the kidney. The anterior pair are elongated, and correspond usually to three or four segments. These bodies are in close relation to the ganglia of the sympathetic chain, and contain large numbers of chromaphil cells, though they appear not to be made up entirely of them.

The inter-renal body [Figs. 15, 16, 17, and 18 (*i.r.*)] is an "ochre-yellow" rod-shaped structure, paired in the rays, unpaired in the dogfishes and sharks, lying usually in the region of the posterior part of the kidney, but sometimes extending as far forward as the anterior extremity. It bears a striking resemblance in its colour, general appearance,

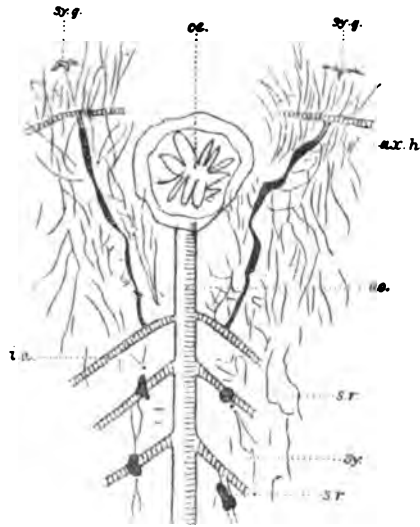


FIG. 16.—From the same preparation as Fig. 15. First three suprarenals of each side.

Lettering common to Figs. 16, 17, 18, 21, and 22.—*a.a.*, axillary artery; *a.i.r.*, anterior broken-off portions of the inter-renal body; *ao.*, aorta; *ax.h.*, anterior pair of suprarenal bodies; *h.k.*, head kidney; *i.a.*, intercostal arteries; *i.r.*, inter-renal body; *k.*, kidney; *l.k.*, lobe of kidney substance; *æ.*, oesophagus out across; *s.r.*, suprarenal bodies; *sy. g.*, sympathetic ganglion; *sy. pl.*, sympathetic plexus.

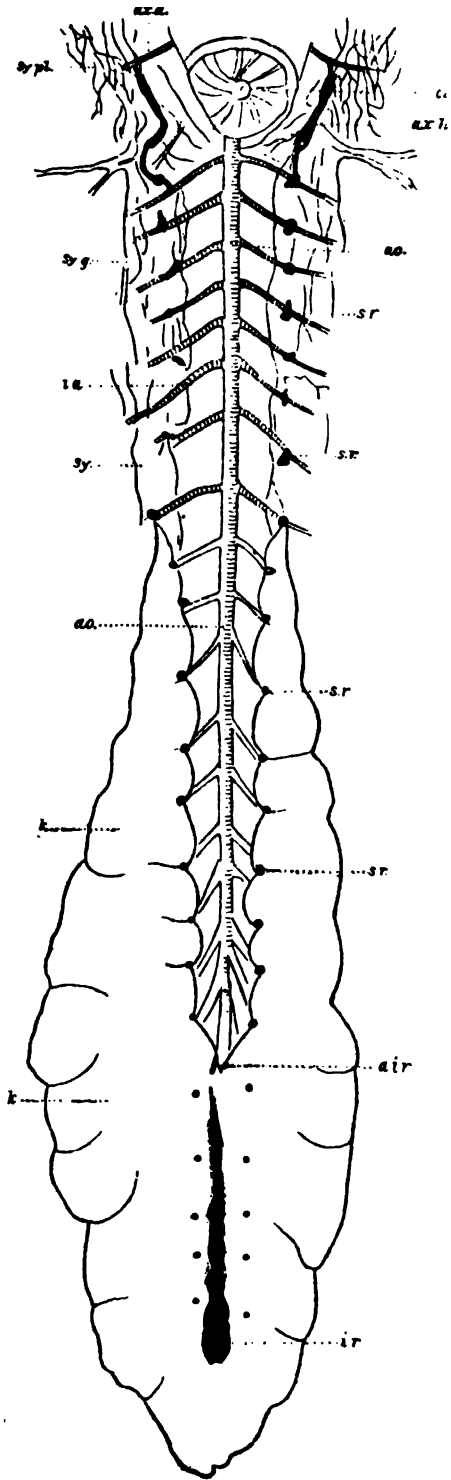


FIG. 17. — Ventral view of kidneys, "suprarenals," and inter-renal of *Scyllium castus*. This drawing shows fairly well the relations to the sympathetic. There is a large plexus anterior to and outside the first paired body ("axillary heart") with ganglia here and there. ( $\times \frac{1}{2}$ .)

Lettering same as for Fig. 16.

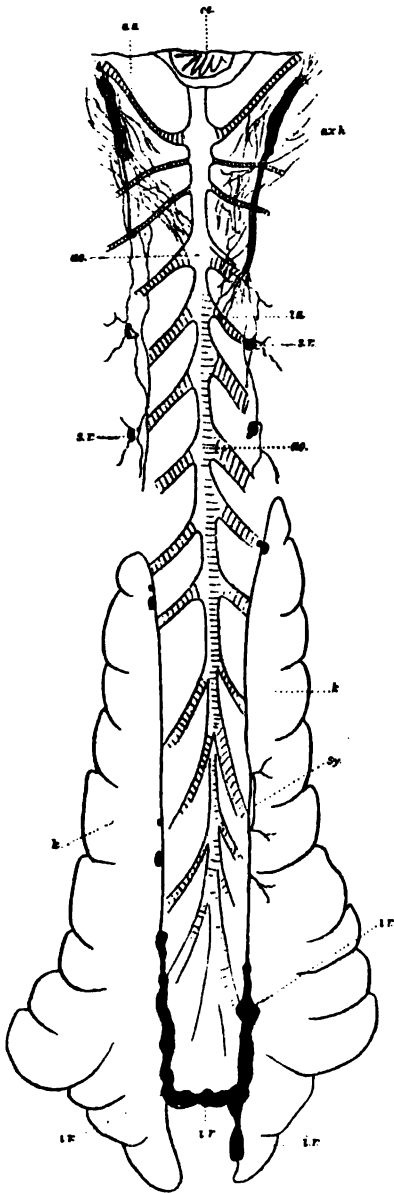


FIG. 18.—Ventral view of kidneys, etc., of *Raja batis*. This drawing represents a not unusual condition in the rays, in which there is bridge-like communication between the inter-renals of the two sides. The sympathetic is shown to some extent to about the middle of the left kidney.

Lettering same as for Fig. 16.

and relations to the kidney, to the adrenals of the Anura, and in the first two of these features to those of the Reptilia. The body consists of cells which have the same



general appearance and the same micro-chemical reaction as the "corpuscles of Stannius," the cortical adrenals of Teleostean fishes, and the cortex of the adrenals of higher vertebrates.<sup>1</sup>

The effect of injection into the venous system of a mammal extract made from the "paired bodies" of Elasmobranchs is shown in Fig. 19. It will be seen that there is a very marked rise of the arterial blood-pressure. In Fig. 20 is seen the effect of the injection of an extract made from the inter-renal. There is a certain effect upon the blood-pressure which can be readily explained as the result of more or less admixture with "medullary glands" in making the extract.

In Teleosts the cortical adrenal bodies are usually paired, round or oval, pale pink bodies, placed on the spinal or ventral surface of the kidney. They are near the posterior extremity of the renal mass, and are either free on its surface or more or less embedded in its substance (see Figs. 21 and 22). The constituent cells are of the same character, and have the same arrangement as those of the inter-renal of Elasmobranchs. It is now fully ascertained that these structures (the "corpuscles of Stannius") in Teleosts represent the inter-renal of Elasmobranchs [Swale Vincent (720, 722, 728), and other papers; Diamare (210, 211); Srdinko (660, 661)]. It had been erroneously considered by some authors that the modified pronephros of Teleosts represents the adrenal body in these fishes.<sup>2</sup>

A very important discovery has recently been made by Giacomini (311, 312, 313), who finds that the corpuscles of Stannius are not the only representatives of cortical adrenal substance in teleostean fishes. He has worked out the subject especially in many fishes of the eel tribe, and finds isolated bodies on the cranial border of the "head kidney," on the anterior and posterior cardinal veins, which he considers are to be regarded as of the same general nature as the corpuscles of Stannius, though they present certain

<sup>1</sup> See also Grynfeldt (334, 335, 336, 337, and other papers).

<sup>2</sup> Since this view has now been completely abandoned, there is no need to revive the controversy. It was Rathke (599) who first put forward this theory, which was later revived by Weldon (744). The view was proved to be untenable by the present writer in 1895 (728). For a recent full account of the discussion, see H. Poll (586).

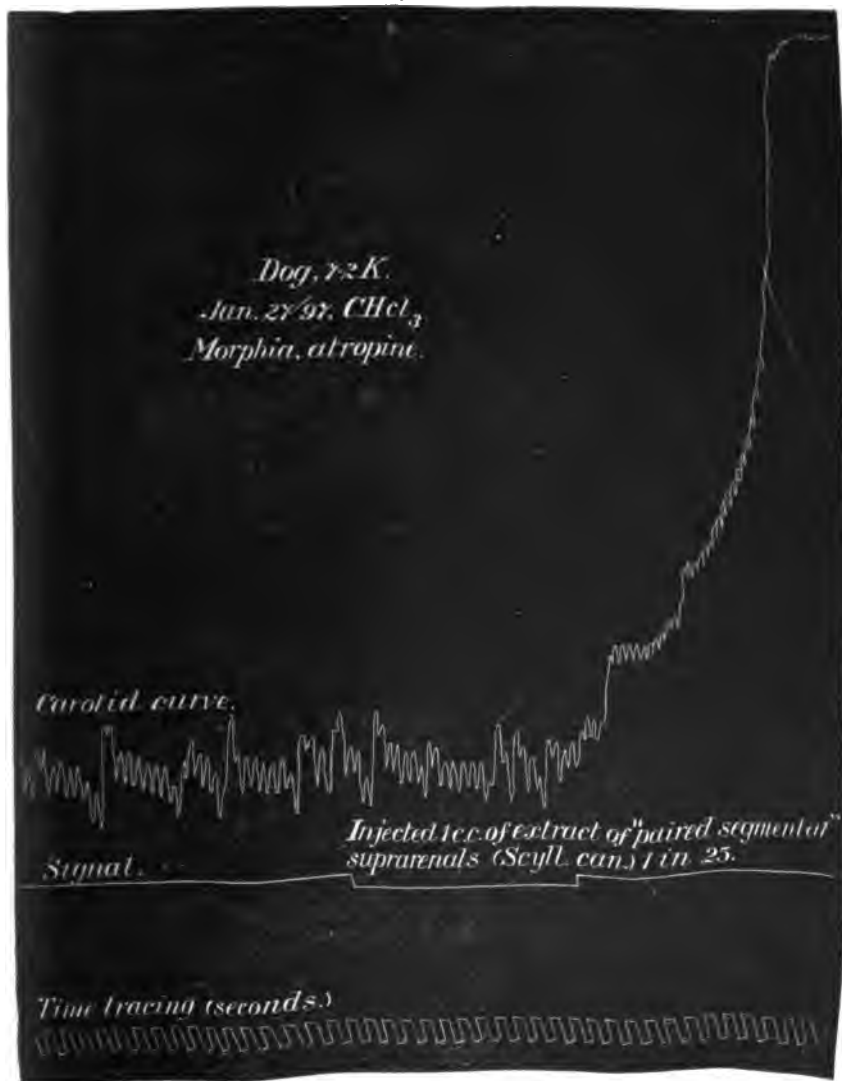


FIG. 19.—Effect of injection of 1 c.c. of extract of "paired segmental suprarenals" (1 in 25) taken from *Scyllium canicula*. It will be seen that the rise of blood-pressure is very striking.

slight differences (313). So that in teleostean fishes we have now to consider a "cranial" and a "caudal" cortical body. This is of the greatest importance as bearing upon certain experimental investigations (*vide infra*, p. 148).

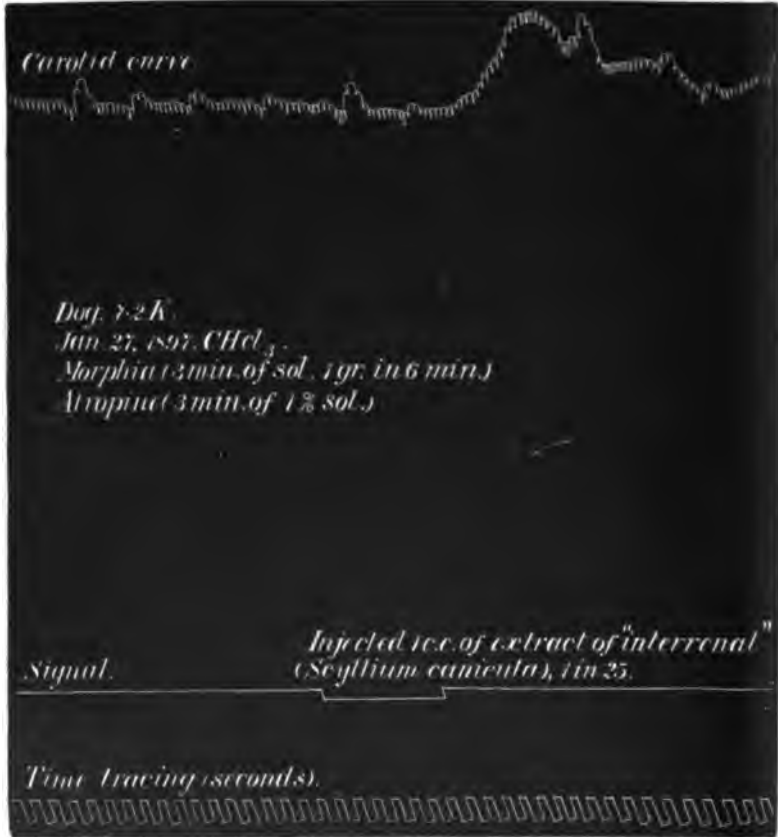


FIG. 20.—Effect of injections of 1 c.c. of extract of "inter-renal" (1 in 25) taken from *Scyllium canicula*. It will be seen that there is a certain small rise of the arterial blood-pressure. This is not at all comparable with that produced by an extract of the "paired bodies" (see Fig. 17), and is to be explained by the fact that in extracting the inter-renal from the body it is almost impossible to avoid removal also of some of the "paired bodies."

To Giacomini also belongs the credit of having discovered the chromophil or medullary structures in teleostean fishes. They consist of cells which stain brown with salts of chromium in the walls of the cardinal veins, especially on the

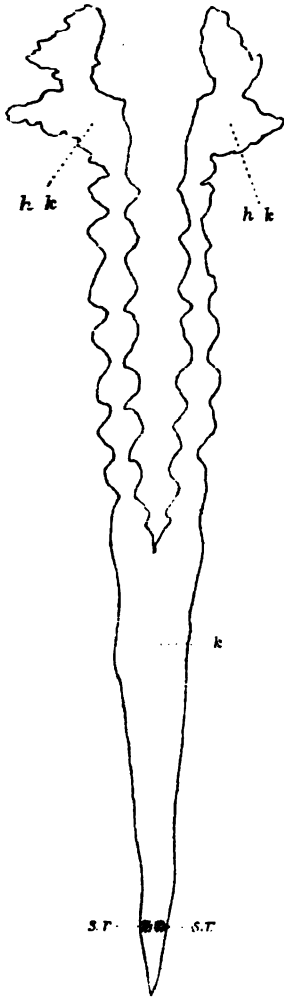


FIG. 21.—Kidneys and cortical adrenals (corpuscles of Stannius) of *Pagellus centrodontus*. The adrenals are on the spinal surface, shown by the dotted lines.

Lettering same as for Fig. 16.

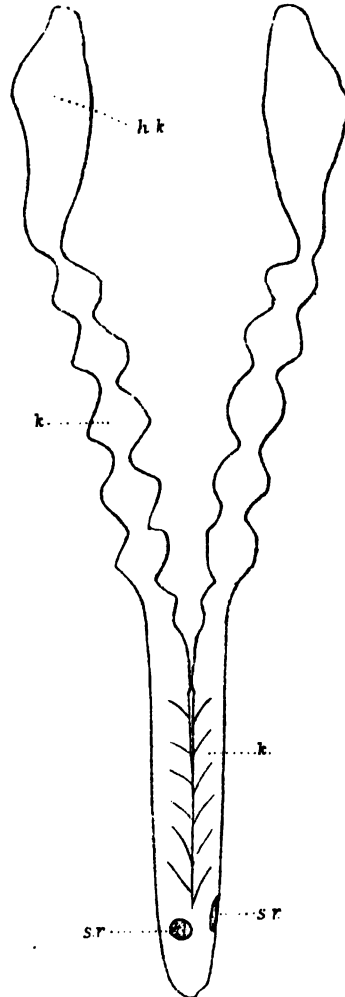


FIG. 22.—Kidneys and cortical adrenals (corpuscles of Stannius) of *Gadus morrhua* (ventral view). One body is on the ventral surface, the other half-way round towards the spinal surface.

Lettering same as for Fig. 16.

right side and towards the cranial end of the body, along the lymphoid tissue of the head kidney. The groups of cells are disposed between the lobes of the cranial cortical

body [Giacomini (305, 309)]. These had often been searched for by previous observers, but in vain [see especially Moore and Vincent (516, 517)].

In Ganoids the cortical representatives were noted by Stannius (664) in 1846. He describes them as small whitish or yellowish bodies scattered throughout the substance of the kidney and forming alveoli, whose cells stain black with osmic acid (see Fig. 25). Quite recently Giacomini (308) has described chromaphil elements in the walls of the cardinal veins and the venal renales revehentes.

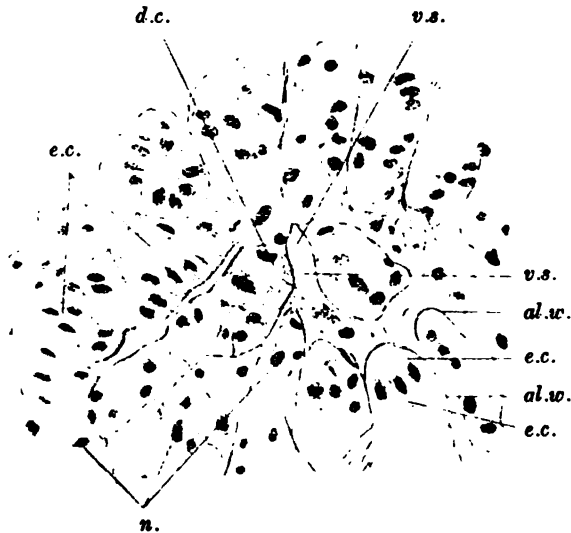


FIG. 23.—Section of the inter-renal body of *Raja clavata*, showing "alveoli" of various shapes and sizes, filled with cells, many of them elongated.

*al. w.*, walls of "alveoli"; *d.c.*, cells resembling "demilune" cells; *e.c.*, elongated cells; *n.*, nuclei; *v.s.*, venous sinuses.

The question as to the existence of adrenal bodies in the Dipnoi has long been under discussion. In *Protopterus annectens* Parker (554) describes "around the kidney, but more particularly along its dorsal and outer sides, masses of brown cells, which in appearance remind one of the adrenal bodies of Amphibia," and he suggests the inquiry "whether they or the lymphoid cells which give rise to them have anything to do with the adrenals." In 1895 the present writer (728) examined this point with some care, and came to the conclusion that this tissue—a large-celled

adenoid tissue—has nothing to do with the adrenal bodies, and this notwithstanding that in some regions it has a very “epithelial,” a very “glandular,” appearance.

Pettit (567) in 1896 claimed to have found the adrenal bodies in Protopterus. He says that in general form and relations they resemble those of Teleostei. He gives no drawings, makes no mention of any distinction between cortical and medullary bodies, and, indeed, gives no evidence

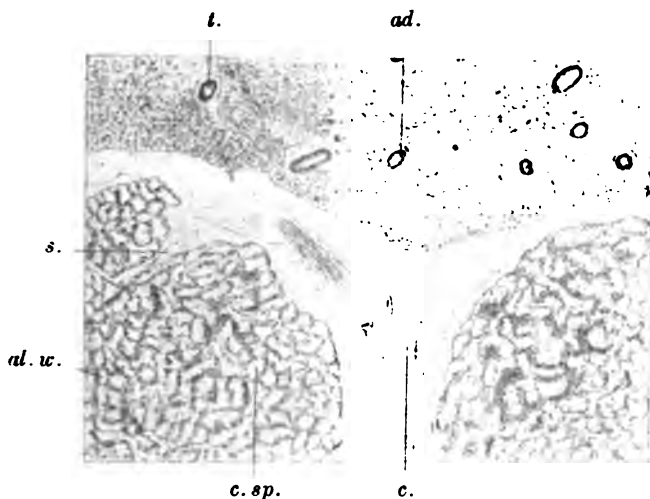


FIG. 24.—Section through a portion of the kidney and the two cortical adrenals (corpuscles of Stannius) of *Conger conger*, showing the renal inter-tubular material, the low-power appearance of the adrenals in this species, and their connections with the kidney. ( $\times 70$ .)

The appearance of hollow spaces in the centre of the groups of cells in this species is apparently due to the fact that the central cells are more difficult to fix, and very susceptible to rapid post-mortem changes.

*ad.*, adenoid tissue of kidney between the tubules; *al. w.*, walls of “alveoli”; *c.*, capsule; *c. sp.*, central space in “alveoli”; *s.*, septa; *t.*, tubules of kidney.

that he found anything which could lay claim to consideration as belonging to the adrenal system.

Wiedersheim (746, 747) has recently described certain structures in Protopterus which he thought were the chromophil bodies. The tissue he describes is placed dorsally and menially to the posterior cardinal veins.

Giacomini (310), by a careful study of serial sections, has come to the conclusion that the bodies described by Wieder-

sheim as adrenals are the pulmonary branches of the vagus nerve, and that the vessels he interprets as the posterior cardinal veins are in reality the pulmonary arteries.<sup>1</sup> In the same communication Giacomini claims to have discovered the true chromaphil bodies arranged segmentally round the intercostal arteries and in the wall of the cranial part of the posterior cardinal vein and the vena azygos dextra. He believes that the inter-renal body (cortical representative of the adrenal) is absent in this species of the Dipnoi, and renews Parker's suggestion that it may be replaced functionally by the adenoid tissue.

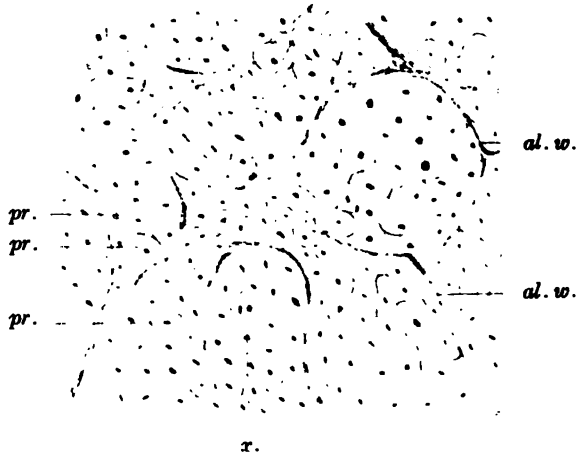


FIG. 25.—Section of an adrenal body (corpuscle of Stannius) of the sturgeon (*Acipenser sturio*). The "alveolar" arrangement is well seen, and the cell outlines are distinct.

*al. w.*, walls of "alveoli"; *n.*, nuclei; *pr.*, granular protoplasm.

It seems extraordinary that there should be no representative of the adrenal cortex in the Dipnoi. The present writer has from time to time dissected specimens of *Protopterus*, and has examined series of sections of this fish and of *Lepidosiren*, but has never been able to detect any organ or tissue which seemed likely to correspond to adrenal cortex. If the tissue originally described by Parker is in reality adenoid tissue, we should hesitate to ascribe to it any secretory function. The perirenal tissue is, however,

<sup>1</sup> This discussion shows how far removed from the mammalian morphology is the disposition of the adrenals in the Dipnoi.

very extraordinary in appearance, and deserves careful consideration.

It is obvious that the subject of the adrenal bodies in the Dipnoi demands further investigation.

The adrenals of Amphibians are intermediate in many respects between those of higher and lower vertebrates. In the Anura the adrenals are golden-yellow streaks on the ventral surface of the kidney, of about 15 millimetres in length in the frog to about 28 millimetres in a good-sized toad. Their width varies in a similar manner from 1 to about 3 millimetres. But their dimensions vary very considerably according to the size and development of the particular individual.

In a good specimen the adrenals present a beautiful appearance, forming on each side a series of irregular arcs with their convexity outwards, and varying in width from place to place. Their colour is a bright golden yellow, of a somewhat fatty aspect, and their surface is marbled with veins. In both frogs and toads, although the body reaches nearly to the anterior end of the kidney, it always ceases at a point anterior to the posterior fifth of the organ.

In the Urodela the adrenal is broken up into a series of strips and islets which extend not only the whole length of the kidney, but also anteriorly to that organ, as far forwards as the origin of the subclavian artery.

The microscopic structure is practically the same in Anura and Urodela. The gland is seen at once to consist of two distinct kinds of structure. The greater part is made up of cell columns, which are of varying size and shape, and which interlace in all directions. The cells are of different shapes, but mostly elongated and tapering, and they contain a large round nucleus, which stains very deeply with hæmatoxylin. This structure is the "cortical," which corresponds to the "inter-renal" of Elasmobranchs, the corpuscles of Stannius ("cranial" and "caudal" series) of Teleosts and the cortex of Mammalian adrenal (see Figs. 26 and 27).

But in addition to the above-described structure, we get masses of a different kind of cell. These are often at the borders or ends of the cell columns, but are otherwise irregularly distributed. In the islets anterior to the kidney



in the Urodela these masses of cells are more numerous, and some of the islets are made up entirely of them. This structure is analogous to the paired suprarenal bodies of the Elasmobranch fishes and the "medulla" of the adrenals of higher vertebrates. It consists of chromaphil cells. Thus in the Amphibia we have transition stages between the single adrenal of higher vertebrates and the total separation of the two constituents in the Elasmobranch fishes<sup>1</sup> (see Figs. 26 and 27).



FIG. 26.—Section through the kidney of *Rana temporaria*, showing relation of the adrenal to the kidney substance. (Low-power drawing.)

Lettering common to Figs. 26, 27, 28.—*bl. c.*, blood corpuscles; *c.*, cortex; *c.t.*, connective tissue; *g.p.*, granular protoplasm of medullary cells; *i.*, interspaces between cell columns; *k.*, kidney; *k.t.*, kidney tubules; *m.*, medulla; *mal.*, Malpighian bodies; *n.*, nuclei; *p.*, protoplasm of cortical cells.

dulla" are often almost identical with those of birds.

A fairly typical representation of the microscopical appearances of the reptilian adrenal is given in Fig. 28.

Birds show an intimate interlacement of the "Hauptstränge" (cortical) and the "Zwischenstränge" or "Intermediärstränge" (medullary), so that the latter occupy the meshes of the former (see Fig. 29).

Mammals, alone among animals, possess a true cortex and a true medulla, the latter as a rule completely surrounded by the former.

Some idea of the microscopical appearances of the Amphibian adrenal will be obtained from Figs. 26 and 27, which represent sections of the adrenal in the frog and the toad respectively.

#### 4. *Amniota.*

In reptiles the "cortical" and "medullary" constituents enter into closer relationship with each other than in lower vertebrates. In some groups the chromaphil cells are arranged mostly on the dorsal aspect of the gland, and only penetrate to a small extent; in others there is a considerable mixture of the two elements. In the Crocodilia and the Chelonia, for example, the relations of "cortex" and "me-

<sup>1</sup> Swale Vincent (720); Srdinko (659), Giacomini (303, 306).

The cortex has in all essential points the same structure as its homologues in the lower vertebrates—viz., the Hauptstränge of birds, the “cortical” columns of Reptiles and Amphibians, the corpuscles of Stannius of Teleosts, and the “inter-renal” of Elasmobranchs. It consists of rounded groups or columns of cells with one or two vesicular nuclei, and containing glistening fat-like granules. These granules become blackened by osmic acid, and stain deeply with Sudan III. and Scharlach R. They are dissolved

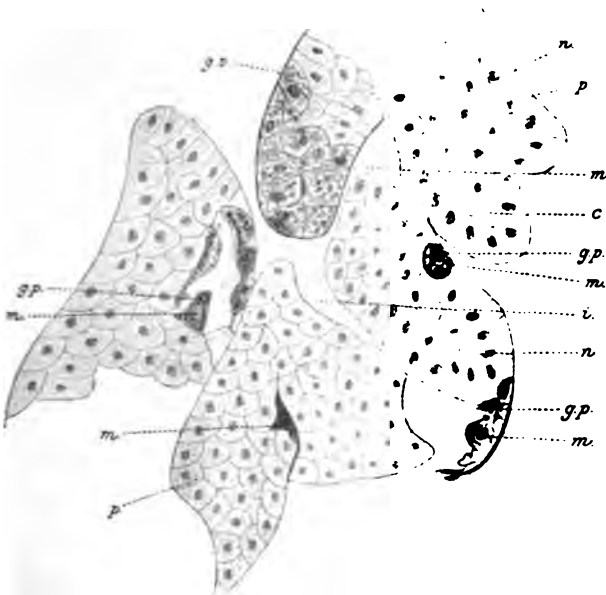


FIG. 27.—Small portion of adrenal of *Bufo vulgaris*. Leitz panchromat., 3.0 mm. (slightly diagrammatic).

Lettering same as for Fig. 26.

by xylol, chloroform, etc., and so, when these reagents are used in the preparation of microscopical specimens, a vacuolated appearance of the protoplasm results.

The structure of the medulla is not so easy either to discover or to describe, but we may say in general terms that it consists of cell columns which are not so distinctly marked as those of the cortex. The cell outlines are not so distinct as those of the cortex, and the granules in the protoplasm have a great affinity for nuclear stains such as hæma-

toxylin, safranin, etc. These granules also reduce chloride of gold and become green in contact with ferric chloride. But their most characteristic reaction is with chromium salts. In the presence of any of these, or of chromic acid itself (in many instances, at any rate), the cells become stained so as to assume any tint between a bright yellow and a dark brown. This reaction was discovered by Henle

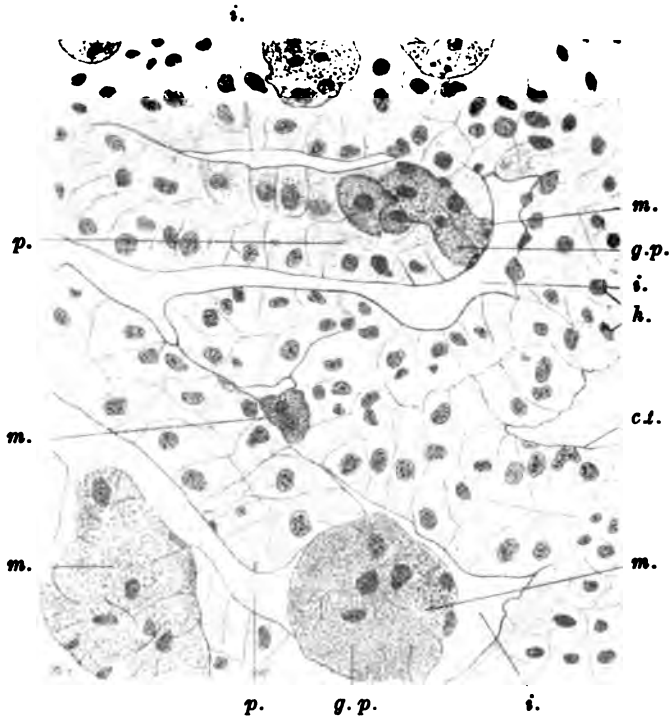


FIG. 23.—Small portion of adrenal of *Uromastix Hardwickii*. Leitz panchromat., 3.0 mm. Drawn with Abbe's camera lucida.

Lettering same as for Fig. 26.

(359) in the year 1865. Stilling (667, 668), who discovered the cells having the same reaction along the sympathetic and in the carotid gland of mammals, called them, the corpuscles which they formed, and the medulla of the adrenal, "chromophil." The modification "chromaphil" will be used throughout.<sup>1</sup>

<sup>1</sup> Kohn, who repeated Stilling's observations, used the term "chromaffin," and called the bodies "paraganglia." More recently Poll has invented still another term, "phaeochrome." There seems to be no need for either of these.

5. *Accessory Adrenals.*

Many important points in the comparative anatomy of the adrenals can be conveniently dealt with under this heading.

The arrangement of the inter-renal and the "paired suprarenals" of Elasmobranchs at once suggests the possi-

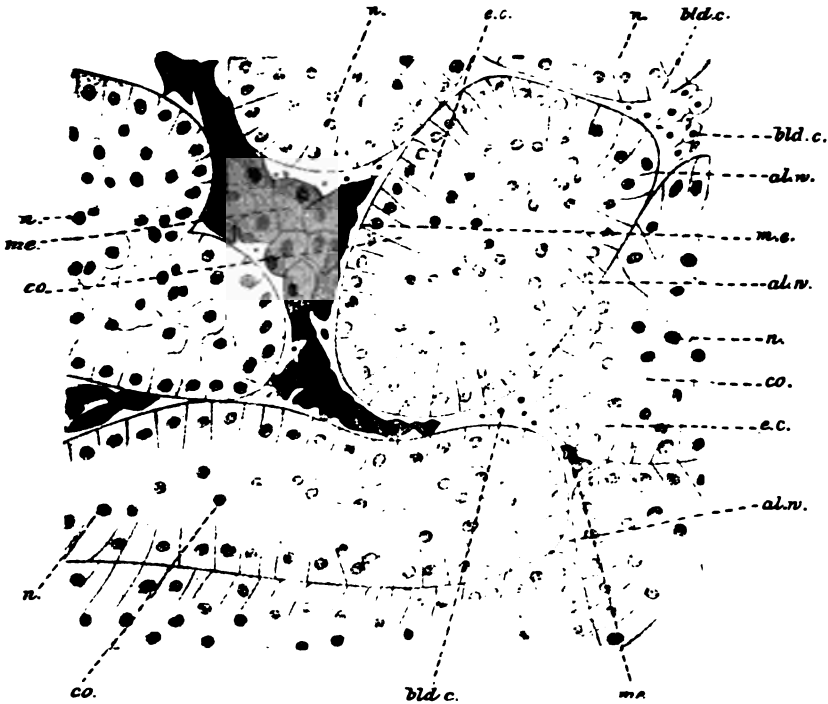


FIG. 29.—Section of the adrenal of *Meleagris Gallopavo*. The material was fixed (Müller's fluid) with acetic acid and stained with hæmatoxylin.

A strand of medullary cells is seen running between the cortical columns.

*al. w.*, walls of "alveoli"; *bd. c.*, blood corpuscles; *co.*, cortex; *e. c.*, elongated cells; *n.*, nuclei; *me.*, medulla.

bility of outstanding portions of both "cortical" and "medullary" constituents being found in the higher as well as in the lower vertebrates. And the same possibility was suspected long ago from other considerations.

The term "accessory adrenal" in mammals has been used in different senses. We must carefully distinguish between :

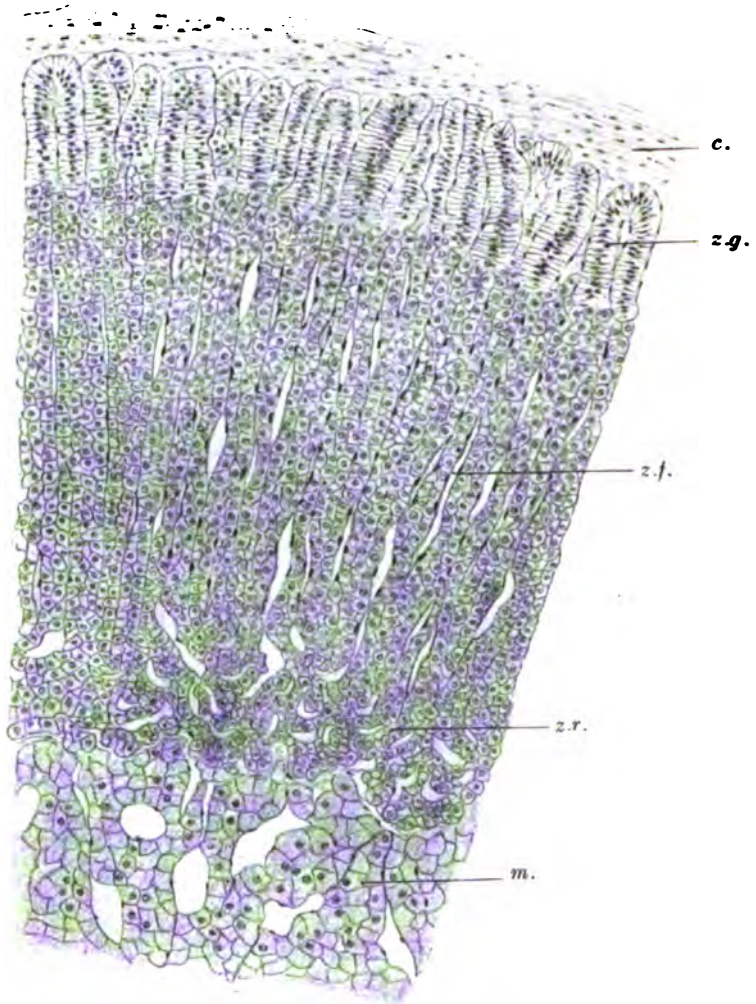


FIG. 30.—Section through portion of the adrenal body of a dog, showing the various zones of the cortex, and the medulla. (Drawn by Mrs. Thompson.)  
*c.*, capsule; *m.*, medulla; *z.f.*, zona fasciculata; *z.g.*, zona glomerulosa (zona arcuata); *z.r.*, zona reticularis.

1. Bodies composed entirely of cortical substance—  
“accessory cortical bodies.”<sup>1</sup>
2. Bodies made up exclusively of medullary substance—  
“chromaphil bodies.”

<sup>1</sup> The term “accessory inter-renal bodies” has been sometimes applied to them, but it seems best to avoid the term “inter-renal” except as applied to the Elasmobranchs.

3. True accessory adrenals composed of both cortex and medulla.

The *accessory cortical bodies* represent by far the larger number of structures which have passed under the name of "accessory adrenals." They often show the three zones characteristic of the cortex of the adrenal of mammals, but no chromaphil cells are present—there is no "medulla." The smallest of these bodies are microscopic; others may reach a diameter of a centimetre or more. They are found in the neighbourhood of the chief adrenal, sometimes embedded in other organs, in the retroperitoneal space, or in the genital region, as, for example, in the ligamentum latum, or in the space between testis and epididymis, where they are known as "Marchand's adrenals."<sup>1</sup>

*The Chromaphil Bodies.*—These are found, or may be found, in any part of the body into which the sympathetic nervous system extends, and more particularly as groups of cells in connection with the abdominal sympathetic and its extensions. In connection with the abdominal sympathetic they were first noted and described by Leydig (463), and called "Kernnester" by Mayer (490). The observations of both these authors applied to the Urodela.

But the recognition of the chromaphil cells and corpuscles in mammals and the characteristic reaction with chromium, by which they are now designated and homologized with the medulla of the adrenals, are due to Stilling (667, 668). This author found in the abdominal sympathetic small bodies composed of cells having the same chromaphil reaction as those forming the medulla of the adrenal. He states that some are nearly a centimetre in length, while others are only just visible to the unaided eye. They are round, oval, or elongated in form, and their thickness is never more than a few millimetres. They have a tunica propria, small vessels and capillaries. Between the capillaries are cells which resemble in all respects those of the adrenal medulla. The resemblance between the chromaphil corpuscles of the sympathetic and the medulla of the adrenal is rendered all the greater by the occurrence in the latter of occasional nerve cells. Stilling found these corpuscles

<sup>1</sup> Marchand (479); see also Pilliet and Victor Veau (577), and Eggeling (232).

in the rabbit, the cat, and the dog, and especially in young animals. He gives details of a method for displaying them.

This extracapsular chromaphil material is still very imperfectly understood by many writers on the physiology and pathology of the adrenals. Thus Rolleston (617) refers to Zuckerkandl's "parasomata"—the carotid body, the coccygeal, and "some cells in the pituitary." Now, the coccygeal body does not contain chromaphil cells, nor

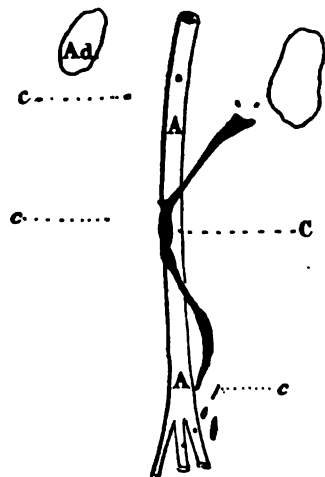


FIG. 31.—Abdominal chromaphil body of an adult dog.

Lettering common to Figs. 31, 32, and 33.—*A.*, aorta; *Ad.*, adrenal; *C.*, abdominal chromaphil body; *c.*, smaller chromaphil bodies.

the pituitary, so far as I am aware. But the writer omits all reference to a very striking mass of chromaphil tissue (the paraganglion aorticum of Kohn)—the abdominal chromaphil body—which is present in the ordinary laboratory animals.<sup>1</sup> The existence of this important body is probably still unknown to many physiologists and anatomists. It can readily be displayed in the dog, for example, by removing the liver and alimentary tract from the abdomen, and placing a piece of absorbent cotton soaked in a solution of potassium bichromate (3 to 5 per cent.) over the retroperitoneal tissues for six to twelve hours. On removing the whole of the remaining tissues and washing in running water for a few hours, the chromaphil bodies are plainly visible, and still more plainly if the whole preparation be placed in glycerin. The "abdominal chromaphil body" is revealed by this method as a very dark brown wavy streak of irregular diameter, placed in front of the aorta and extending from the region of the adrenals in front to the bifurcation of the aorta behind. Other elongated, oval,

<sup>1</sup> It seems possible that the "abdominal chromaphil body" of the dog may correspond to the "Nebenorgan" of Zuckerkandl. But the general shape and appearance of the two bodies are quite different, and Zuckerkandl's body was found only in very young subjects.

or rounded patches or specks of chromaphil tissue are also visible in different regions.<sup>1</sup>

Figs. 31, 32 and 33 will give an idea of the arrangement of the abdominal chromaphil body and other smaller chromaphil corpuscles in the dog, the cat, and the rabbit respectively.

In the dog the extra-adrenal chromaphil tissues are abundant and the abdominal chromaphil body is easily and beautifully shown by the method above described. A few minutes after the mop of absorbent cotton soaked in

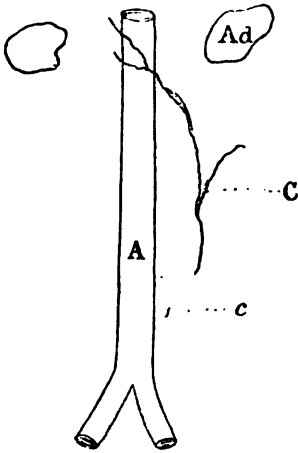


FIG. 32.—Chromaphil bodies of adult cat.

Lettering same as for Fig. 31.

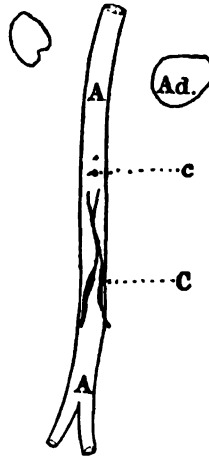


FIG. 33.—Abdominal chromaphil bodies of a rabbit.

Lettering same as for Fig. 31. The principal body is bifurcated anteriorly and posteriorly.

bichromate has been placed over the aortic region a long pale brown strip of tissue may be seen lying over the aorta, and within half an hour to an hour its deep brown stain is fully developed and the relations of the body can be determined. It varies in length in the dogs I have dissected from 1 to 4.5 centimetres, and its width varies from a very fine line to about 5 millimetres.

Numerous irregularly disposed smaller masses of chromaphil tissue are found in different regions more or less closely

<sup>1</sup> I am indebted to the late Dr. Stilling and to Dr. Kohn for their kindness in giving me detailed instructions as to how to find these bodies, and to Dr. Kohn for some specimens which he generously sent me.



related to the principal chromaphil body [see Figs. 31, 32, and 33 (c)].

In the cat (Fig. 32) the chromaphil body tends to consist of long threads of tissue. These threads are stretched along the sympathetic, and the relationship to this nervous system is more obvious than either in the dog or the rabbit.

In the rabbit (Fig. 33) there is a distinct tendency for the principal chromaphil body to be paired, or it may be

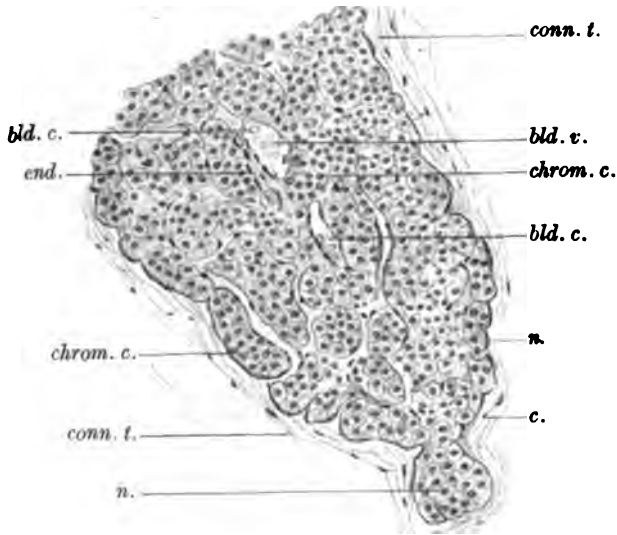


FIG. 34.—Transverse section through the abdominal chromaphil body of the dog. Fixed in corrosive sublimate and stained with hæmatoxylin. Section  $10\ \mu$  in thickness. Zeitz obj. 6. Drawing, ocular.

Lettering common to Figs. 34 and 35.—*bld. c.*, blood corpuscles; *bld. v.*, blood-vessels; *c.*, capsule; *chrom. c.*, chromaphil cells; *col. c.*, columnar cells of adrenal medulla; *conn. t.*, connective tissue; *end.*, endothelium of blood-vessels; *n.*, nuclei.

bifurcated anteriorly and posteriorly [Fig. 33 (C.)]. The threads of chromaphil tissue frequently run close up to, and may even be continuous with, the medullary substance of the adrenal.

In some animals—viz., monkey, pig, guinea-pig, rat, gopher, and squirrel—the present writer has been unable to discover any chromaphil bodies.

In regard to the microscopic structure of the chromaphil

bodies, a detailed description is not necessary.<sup>1</sup> It is, however, desirable to institute some comparisons between the histological appearances of the adrenal chromaphil tissue and this substance as it occurs in other places, as, for example, in the sympathetic ganglia and in the abdominal chromaphil bodies. These comparisons refer to the structures in the dog.

A comparison of Fig. 34 with Fig. 35 will show that the general resemblance between extra-adrenal chromaphil

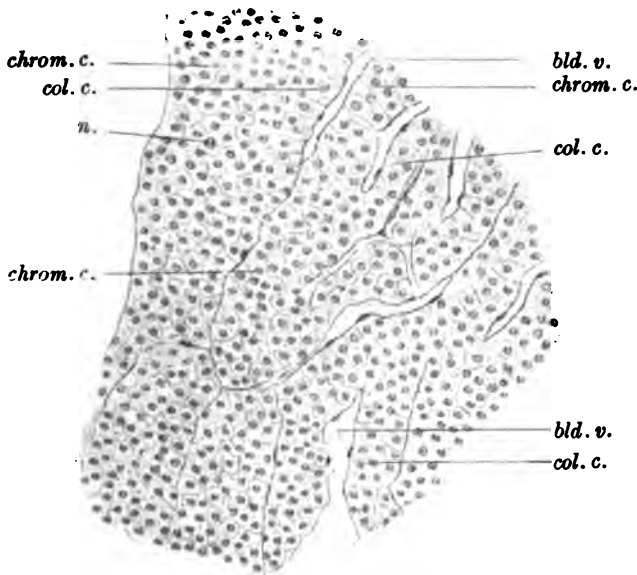


FIG. 35.—Section through the medulla of the adrenal of a dog, prepared as in case of previous figure. Same magnification.

Lettering same as for Fig. 34.

tissue and adrenal medulla is very great. Both consist of columns of cells staining yellow or brown with bichromate of potash. The cell columns are, however, for the most part much thicker in the adrenal than in the abdominal chromaphil bodies. The blood spaces are wider, and the whole aspect gives the impression that the adrenal medulla is more highly organized [see Fig. 35 (*bld. v.*, *col. c.*)].

Many of the cells of the adrenal medulla are spherical,

<sup>1</sup> A full account will, however, be found in a paper by the present writer in the proceedings of the Royal Society for 1910 (731).

as in the abdominal chromaphil body, and their dimensions are the same—viz., about  $12\ \mu$  in diameter. The nuclei, also, are of the same order of magnitude in the two cases—viz.,  $5\ \mu$  or  $6\ \mu$ . But in many regions, especially where the cell columns are separated by large venous sinuses, the cells are arranged in a definitely epithelial fashion round the blood-vessels [Fig. 35 (*col. c.*)]. In this case the cells are columnar in shape, and may reach a length of  $26\ \mu$ , and the nuclei are placed at the end of the cell remote from the bloodvessel.

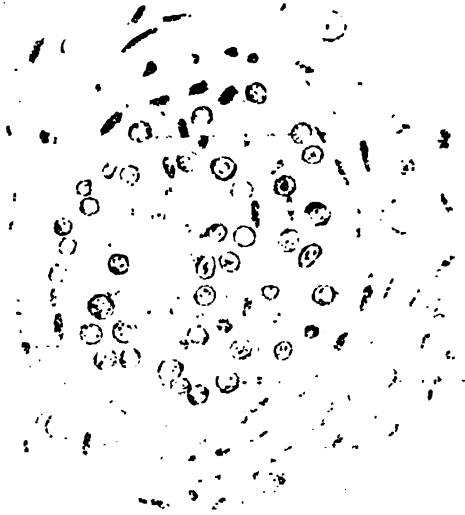


FIG. 36.—Section through a group of chromaphil cells in the inferior cervical ganglion of a dog.

The protoplasm of the adrenal medulla is more distinctly granular than that of the abdominal chromaphil body, and is, moreover, more delicate in consistence, and therefore shows more shrinkage in fixation and tearing during the process of cutting sections. When the adrenal is fixed in bichromate solutions, the section shows vacuoles as do those of the chromaphil body. These are absent in sublimate and Flemming preparations.

Thus it seems justifiable to regard the medulla of the adrenal body as composed of chromaphil cells of the same general character as those forming the chromaphil bodies. But the former have undergone specialization, and the

structure of the substance has become elaborated into an organ with more definitely glandular form.

It is clear from all that has gone before that the extra-adrenal chromaphil tissues contain a substance which gives the same macro- and micro-chemical reactions as adrenin. It has been shown by Biedl and Wiesel (108) that the "parasomata" (Nebenkörper) discovered by Zuckerkandl (774) in the human subject contain adrenin or some substance which has an identical effect upon the blood-pressure. The present writer has recently been able to prove that the abdominal chromaphil bodies of the dog contain the same



FIG. 37.—Dog, 8 kilogrammes. November 10, 1909.  $\text{CHCl}_3$ , morphia, atropin. Carotid blood-pressure. Time in seconds. At the point signalled an extract from the chromaphil bodies of three dogs was injected into the saphenous vein.

or a similar substance. Fig. 37 shows the effect of injecting into the saphenous vein of a dog an extract from the chromaphil bodies of three dogs. It will be seen that there is a very considerable and very characteristic rise of the blood-pressure.

The investigations of Stilling were confirmed and extended by Kohn (406, 413) and Kose (420, 421), who laid stress on the fact that the chromaphil cells are common and typical elements of the mammalian sympathetic system. Kohn's view is that what is ordinarily called the "cortex" of the adrenal is in reality the only part which ought to be called adrenal at all, while the medulla is simply

the "paraganglion suprarenale," a group of what he called "chromaffin" cells, which have become included in the adrenal. This matter will be referred to again later on.

Zuckerkindl (774) in 1901 found in the retroperitoneal space at the origin of the inferior mesenteric artery a pair of large chromaphil bodies, which he called "Nebenkörper des Sympathicus." These he found constantly in the embryo and in the new-born human subject, and, as we have seen, Biedl and Wiesel found that the bodies contained a pressor substance (108).

*True accessory adrenals*, containing both cortex and medulla, like the main gland, are said to occur in the neighbourhood of the abdominal sympathetic, and in the region of the body where the cortical elements first arise.

#### 6. *Tabular Statement of Chief Facts in Comparative Anatomy of the Adrenals.*

The table<sup>1</sup> opposite, modified from Poll (586), will render clear the chief facts in the comparative anatomy of the adrenal system.

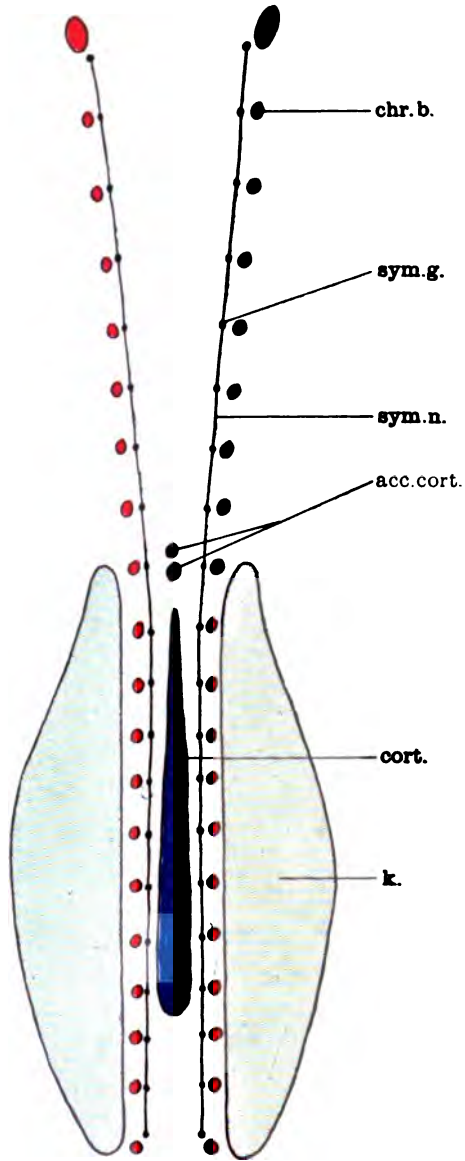
In concluding this section we would call special attention to Figs. 38 and 39, which give in a diagrammatic form a comparison of the adrenal representatives in Elasmobranch fishes and in mammals respectively. The cortical elements are coloured blue, while the medullary constituents are put in in red. In Fig. 39 the groups of chromaphil cells in the sympathetic ganglia are drawn too large.

<sup>1</sup> In the table, the term "cortical system" has been substituted for "inter-renal system" employed by Poll. Each of the alternative terms has a certain and a similar disadvantage, inasmuch as it refers to an anatomical arrangement which is not universal throughout vertebrates, but confined to a single group—the term "inter-renal" being only applicable to Elasmobranchs, the term "cortical" being only applicable to mammals. But it seems on the whole preferable to use the word "cortical," because it refers to the arrangement in mammals which will long continue to serve as the standard of comparison in the organology of the adrenal system.

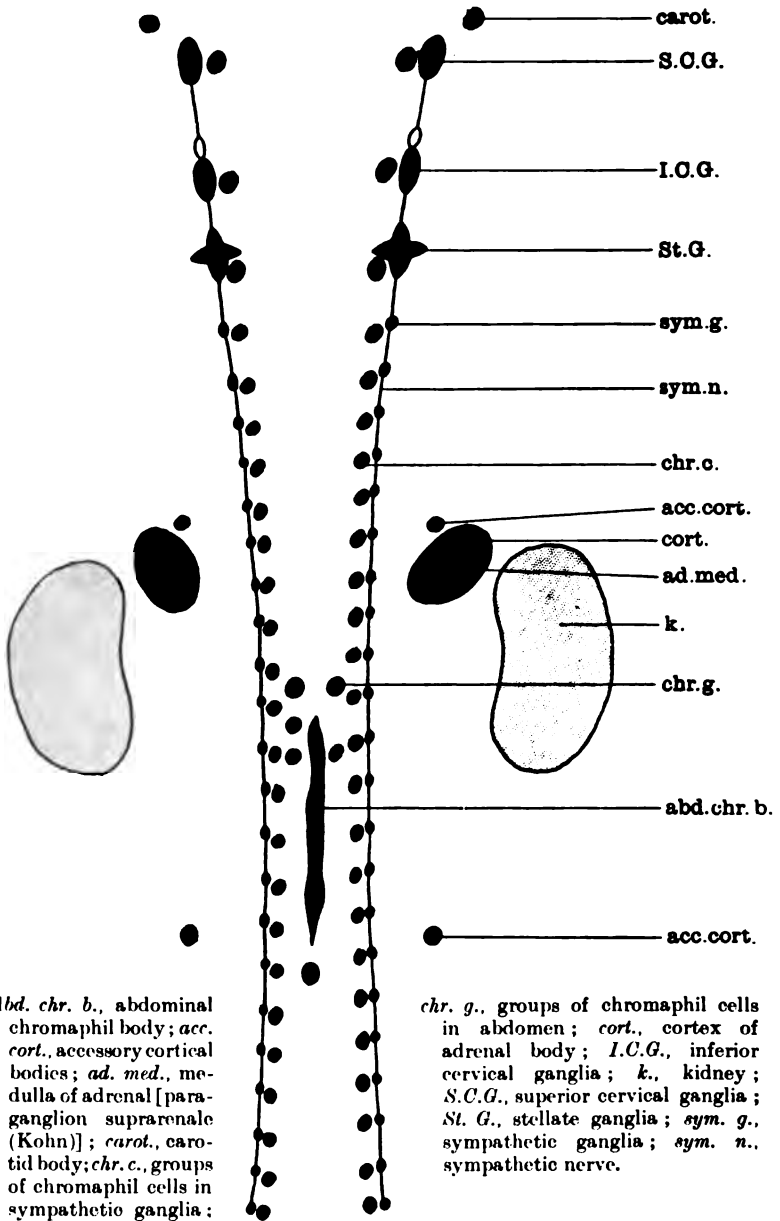
Further, as announced previously, it is proposed to use the term "chromaphil" instead of "chromaffin" or "phæochrome." There is no doubt that in some respects "phæochrome" is the best word, but "chromaphil" is only a slight modification of the original "chromophil" employed by Stilling, and was suggested to me by Professor Schäfer.

It is a pity that we cannot for the "cortical" cells use some name which would describe their staining reaction, or the chemical nature of their contents. But the literature of the comparative anatomy of the adrenals is already overburdened with a complicated and abstruse nomenclature, so perhaps it is best to be content with the term "cortex."

*Acc. cort.*, accessory cortical bodies; *chr. b.*, chromaphil bodies (paired suprarenals) paraganglia (Kohn); *cort.*, cortex of adrenal body (inter-renal body); *k.*, kidney; *sym. g.*, sympathetic ganglia; *sym. n.*, sympathetic nerve.



FIGS. 38 and 45.—Diagram of the adrenal representatives in Elasmobranch fishes, showing the cortical gland (inter-renal body) and the medullary glands (chromaphil bodies, "paired suprarenals") in relation to the sympathetic and the kidneys. The cortical elements are coloured blue, while the medullary constituents are put in red.

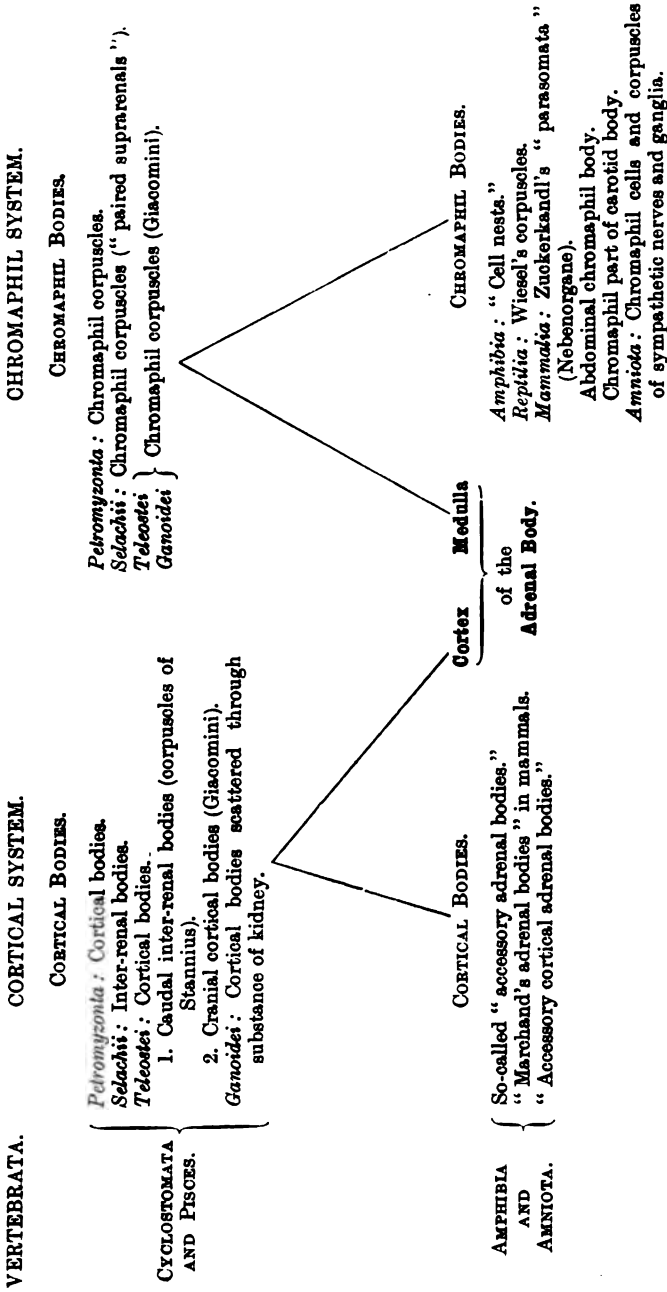


*Abd. chr. b.*, abdominal chromaphil body; *acc. cort.*, accessory cortical bodies; *ad. med.*, medulla of adrenal [paraganglion suprarenale (Kohn)]; *carot.*, carotid body; *chr. c.*, groups of chromaphil cells in sympathetic ganglia;

*chr. g.*, groups of chromaphil cells in abdomen; *cort.*, cortex of adrenal body; *I.C.G.*, inferior cervical ganglia; *k.*, kidney; *S.C.G.*, superior cervical ganglia; *St. G.*, stellate ganglia; *sym. g.*, sympathetic ganglia; *sym. n.*, sympathetic nerve.

FIGS. 39 and 46.—Diagram of the adrenal constituents and outstanding "cortical" and "medullary" (chromaphil) bodies in the mammal, showing the adrenal bodies, the chromaphil cells of the sympathetic and the abdominal chromaphil body ("accessory cortical adrenals") in relation to the sympathetic and the kidneys.

# THE ADRENAL BODIES





### C. Development of the Adrenals.

Balfour (65, 66) expressed the view that "in Elasmobranch fishes we thus have (1) a series of paired bodies, derived from the sympathetic ganglia, and (2) an unpaired body of mesoblastic origin. In the Amniota these bodies unite to form the compound suprarenal bodies, the two constituents of which remain, however, distinct in their development. The mesoblastic constituent appears to form the cortical part of the adult suprarenal body, and the nervous constituent the medullary part." This hypothesis has been fully supported, and the observations leading to it have been completely confirmed by all subsequent work upon the embryology of the adrenals. In the various classes of vertebrates there have been numerous observations, all of them clearly pointing out the totally distinct origin and nature of the cortex and the medulla. It will only be possible to refer to some of the more important papers.

Mitsukuri (509) worked out the development of the adrenal body in the rabbit and in the cat. He concluded that the cortical substance arises from the mesoblast, while the medullary substance is derived from the peripheral part of the sympathetic nervous system, and is at first placed outside of the cortical substance, becoming transported into the middle of the adrenal body in the course of development. That the cortex is derived from the mesoderm and the medulla from the same blastema as the sympathetic ganglia is now universally conceded.<sup>1</sup>

The cortical substance is developed from the coelomic epithelium in a region known as the "adrenal zone." The extent of this zone varies in different vertebrates. In mammals the origin of the cortex appears to be from the coelomic epithelium on either side of the root of the mesentery or a little caudalwards from the cranial end of the primitive kidney, appearing first as a series of buds which subsequently grow together.

In regard to the development of the medulla of the adrenal body, it has been ascertained that certain cells derived (along with the sympathetic generally) from the

<sup>1</sup> See footnote <sup>1</sup>, p. 123.

neural ectoderm, do not develop into nerve cells, but into chromaphil cells. In the anamnia below the amphibia, these do not enter into any relations with the cortical elements, but remain as chromaphil bodies or corpuscles. In Amphibia and in the Amniota some of these chromaphil cells grow into the cortical gland and form its medulla.<sup>1</sup> Ultimately these acquire the chromaphil substance. It is stated that this is not actually found in them in man until some little time after birth,<sup>2</sup> but it occurs in the embryo of the ox and the sheep long before birth.<sup>3, 4</sup>

#### D. Addison's Disease and the Pathology of the Adrenal Bodies.

##### 1. *Introductory and Historical.*

The medical practitioner directs his inquiries towards experimental physiology and pathology in order to ascertain how far modern research will enable him to understand the clinical phenomena of Addison's disease, and to treat his patients in a scientific spirit. On the other hand, the physiologist is eager to acquire whatever information can be derived from the realms of clinical pathology and pathological anatomy, as to the functions of the adrenal bodies. The fuller and more accurate is our knowledge of diseased conditions of the organs, the sounder will be our progress in both these conditions. Pathology has taught us something of the adrenals, and physiology has contributed certain facts of primary importance. It must, however, be admitted that it is not possible at the present time to combine the knowledge derived from

<sup>1</sup> A few authors have in the past held different views. Thus Gottschau (323, 324, 325) and Janosik (379, 380) denied the nervous origin of the medulla, and stated that this is formed from the cortex. Creighton (191, 192) even went so far as to say that "the distinction between the cortex and medulla of ordinary anatomy is quite arbitrary, as there is no real difference between their constituent cells." This view, contrary to all evidence, and only requiring the most casual observation in order to be refuted, has, nevertheless, been supported by Rolleston (616) so recently as 1895, and by Aichel (32 and other papers) in 1900!

<sup>2</sup> Moore and Purinton (514).

<sup>3</sup> Langlois and Rehns (445), and Svehla (681).

<sup>4</sup> The following are some of the more recent papers dealing with the development of the adrenal bodies: Soulié (655, 656), Srdinko (659, 660, 661), Poll (584), Hoffmann (362), Atkinson (55), Wiesel (751, 753), but see especially Poll 586, in Hertwig's "Handbuch."

these two sources in such a way as to give an intelligent explanation of the functions of the adrenal bodies, and at the same time to offer a satisfactory explanation of the symptoms of Addison's disease.

Addison's disease is characterized by the cardinal symptoms of extreme muscular weakness, nausea and vomiting, and an exaggeration of the normal pigmentation of the skin.

Addison (27, 28, 29) attempted to elucidate the nature of a malady which he had styled "idiopathic anæmia," from an inability to associate it with any exact pathological condition. He was thus led to the discovery of the diseased state of the adrenal bodies, and the association between this diseased state and the train of symptoms which bears his name.

The observations were confirmed but not much extended by Wilks (764, 765, 766, 767), Trousseau (698), and Greenhow (331). It was Trousseau who first used the term "Addison's disease." It must be admitted that comparatively little has been added to our knowledge of the clinical aspect of the disease since it was first described by Addison [Rolleston (617, b)].

Addison considered that any lesion of the adrenal bodies which would interfere sufficiently with their function would give rise to the disease. Wilks and Greenhow were, however, of a different opinion—viz., that the true morbus Addisonii has essential peculiarities of its own, that no other disease or degeneration of the adrenal bodies is capable of producing the same associated train of symptoms [Note by editors of Addison's works, New Sydenham Society (29)]. The modern view is entirely in accordance with that first expressed by Addison, that the symptoms are due to an interruption to, or a deficiency of, the functional activity of the adrenal bodies.

## 2. *Symptoms.*

1. *Pigmentation.*—The pigmentation is very variable both as to its period of onset and as to its intensity. Usually it first occurs at a later period of the disease than the general symptoms, such as the muscular prostration. It sometimes occurs only shortly before death, and in some

cases it never occurs at all. Occasionally, however, the pigmentation has been stated to precede the general symptoms.

As for the degree or intensity of pigmentation, it may vary from the dark hue of the negro to a faint sunburn brown. It is very interesting to note that the pigmentation is an exaggeration of the normal, and occurs most markedly in those parts which are normally pigmented, such as the dorsal surface of the forearm, the axillary folds, the areola around the nipples, the genitals, and the groins. The pigmented regions have no sharp margins. Friction or pressure induces especially the increased pigmentation; thus we find dark patches or streaks brought about by corset, belt, garters, braces, or collar-stud.

Pigmentation is usually first noticed on the face, neck, and backs of the hands and fingers, especially over the joints. The lips may sometimes become pigmented and the tongue occasionally presents stains near the free border. There are also to be seen in some cases small, well-defined specks, like small moles, but occasionally of inky blackness. Pigmentation of the peritoneum and pia mater has been recorded. The hair may become darker, but the skin of the hairy scalp and other regions covered by hair does not appreciably change in colour. The linea alba may become a dark line. Rolleston (617, *b*) says that the palms of the hands and the soles of the feet are very rarely pigmented, but he has twice seen pigmentation of the palms with intensification along the various lines.

Microscopically the pigment is found in the cells of the stratum Malpighii, and the dermis shows a few pigmented cells—"carrier cells"—which, it is thought, convey the pigment from the bloodvessels of the dermis to the stratum Malpighii [Schäfer, quoted by Greenhow (331), and Rolleston (617, *b*)].

2. *Asthenia*.—Many authors regard the asthenia or muscular weakness as the most constant and the most significant of all the symptoms of Addison's disease. The patient suffers from an almost complete indisposition for any exertion. He is very easily tired, and is never able to get properly rested. There is no corresponding emaciation or neuritis.

Asthenia is almost always the earliest sign of the disease. Long before one notices any change in the skin the patient complains of extreme lassitude. He can perhaps make

a short series of movements with some energy, but he is almost immediately fatigued. Langlois (439) lays great stress on this feature, and recommends the use of Mosso's ergograph as an instrument of diagnosis. He states that what characterizes the patient with Addison's disease is not so much the loss of ability to perform a single muscular feat, as a more or less complete disappearance of resistance to fatigue. If one submits under the same conditions a patient with Addison's disease, and another patient in a comparable condition (both, for example, tubercular to the same extent), to the ergographic test, we find that the fatigue curve is quite different in the two cases. We find that the simple tubercular patient can carry out a sustained labour (lift a weight of 1 kilogramme every two seconds) for a certain time; but the patient with Addison's disease, who at first will lift the same weight to the same height, soon becomes exhausted; his curve shows a rapid fall. Langlois (439) gives a series of illustrative tracings.

3. *Other Symptoms.*—The majority of authors report that in Addison's disease the blood-pressure is remarkably low. The heart is feeble in action; there is a small, soft, almost imperceptible, pulse. The blood-pressure is stated by Rolleston (617, *b*) to be often as low as 60 to 65 millimetres Hg. On the other hand, Janeway (378) and Dr. J. A. Gibson quote cases in which the blood-pressure is not low.

The temperature is usually subnormal.

There does not appear characteristically to be anæmia, though the patients present an anæmic appearance. It is stated that there is no very marked emaciation in the majority of cases.

Vomiting is very common, and there is frequently hiccup and sometimes diarrhœa. But there may be constipation from loss of muscular tone.

Various symptoms referable to the nervous system have been described. Some of these, such as twitchings and convulsions, point to irritation of the nervous system, but the most characteristic, such as a diminished or absent knee-jerk, are indications of depressed activity of the nervous system. Headaches and faintness are not uncommon.

There seems to be actually a diminution of the urinary pigments.

### 3. *Etiology and Onset.*

The disease is rare. It is commoner in women than in men, and occurs about the thirtieth year on the average. The adrenal bodies may become infected in tubercular patients from the mesenteric glands or from the disease of the vertebræ. But the adrenal bodies themselves seem to be very susceptible to tubercular infection, and are often the only seat of tubercular infection in the body.

Strains and injuries to the back or blows on the abdomen have sometimes been alleged to be the cause of the mischief. In these cases the trauma might render the gland more liable to infection. Traumatic hæmorrhage into the substance of the gland has been stated to be the starting-point of the lesion in some cases.

The onset is nearly always insidious and gradual. Gastric trouble is perhaps one of the commonest causes of the patient's seeking advice. Very rarely the disease seems to come on suddenly after a shock or some cause of worry.

### 4. *Metabolism in Addison's Disease.*

Owing to the rarity of Addison's disease, little is known as to the general (total) metabolism. Nor have we any *a priori* grounds for assuming that this would be either increased or diminished.

According to a brief account given recently by Richter (605), the protein metabolism is not appreciably affected [Kolisch and Pichler (416)]. Senator (644) and Pickardt (576) observed either nitrogenous equilibrium or, with abundant food, nitrogenous gain. On administration of adrenal substance to the patient there was no increase of protein destruction.

There is an increase in the phosphoric acid elimination [Vollbracht (735), Eiselt (236)]. Richter (605) suggests that this has to do with increased destruction of bone substance, though Senator (644) found the calcium elimination not raised.

Nothing certain is known of any change in carbohydrate metabolism. We might expect, since adrenin pharmacodynamically induces glycosuria, that in Addison's disease, where there is presumably a deficiency of this substance,

we should find a lowering of the sugar content of the blood. In experiments upon animals, after extirpation of the adrenal bodies, this is actually found to be the case [Porges (795)],<sup>1</sup> but the clinical evidence in the case of the human subject is meagre and conflicting.

#### 5. *Morbid Anatomy.*

In Addison's original paper eleven cases are recorded. In five of these there was caseous tubercle in both adrenal glands, and in one case tubercle was only present in one gland. One case seems to have been an example of cirrhosis and atrophy. In three cases there were secondary carcinomatous growths in the adrenals, bilateral in one case, unilateral in the other two. In one additional case there was a secondary nodule of carcinoma blocking the right suprarenal vein, and associated with hæmorrhage into the corresponding gland, but there were no growths in either.

Bittorf (112) states that in all cases there is disease of both adrenals. This may be (1) simple atrophy, or (2) inflammatory atrophy (chronic interstitial inflammation) with shrinkage and destruction of the parenchyma, resembling cirrhosis. According to this author, there is no special part of the gland which is of prime importance to life. He considers that the adrenal bodies are single organs, clearly essential to life, interference with which causes a definite train of symptoms. From the tone of this writer it would appear that he does not clearly recognize the essential and fundamental difference between the cortex and the medulla, nor does he appear to fully appreciate the significance of the fact that even if cortex and medulla do really constitute one physiological structure, there are outstanding masses of both constituents in different regions of the body, concerning which it would be out of the question to make a similar hypothesis. There may yet be discovered some reason for looking at the adrenal gland (cortex and medulla taken together) as a functional whole, but Bittorf appears to have come to this conclusion simply because the experimental evidence as to the respective importance to life of cortex and medulla is conflicting,

<sup>1</sup> See also Schwarz (642), Kahn and Starckenstein (390); Kahn (388), Pitres and Gautrelet (578), Beuttenmüller u. Stoltzenberg (97).

and because pathologists have never yet been able to determine any difference in those cases where chiefly cortex or chiefly medulla have been involved.

Winkler (768) gives an account of twenty-four cases of adrenal tumours. There were thirteen primary growths (ten epitheliomata and three sarcomata), and eleven secondary cases. In only two cases was there any bronzing of the skin. From a careful study of these cases the author is quite unable to decide whether Addison's disease is due to an affection of the cortex or of the chromaphil tissue and the sympathetic, or is to be attributed to a lesion of both together.

In cases of Addison's disease a fibro-caseous condition of tubercular origin is by far the commonest condition found. In addition, simple atrophy, chronic inflammation, malignant disease, extravasation of blood, and lesions of the semi-lunar ganglia have been recorded [Phillips (575); Simmonds (649)].

Wiesel (754 to 757) has described in six cases of Addison's disease severe degenerative changes and destruction of the chromaphil cells not only in the adrenal medulla, but also in the sympathetic. He reports, further, that in a case of tuberculosis of both adrenal bodies, where there had been no symptoms of Addison's disease, not only was there no destruction, but there was a hyperplasia of the chromaphil tissues. Wiesel, then, regards Addison's disease as due to a primary lesion of the chromaphil tissues. It is clear that such cases were easily overlooked by the earlier pathologists, and may account for some of the reports of Addison's disease without lesion of the adrenals.<sup>1</sup>

### 6. Pathogeny.

The theories as to the pathogeny of Addison's disease may be divided into two groups: (1) Nervous, (2) chemical or glandular.

If we except Addison's original view (which he somewhat modified later on) and the theory that the adrenals are of no importance in the economy, most of the early theories

<sup>1</sup> Other papers on the pathology of the adrenals are: Bittorf (113), Brodnitz (139), Materna (487), Rössle (614), Goldzieher (320), Parodi (555), Hecht (355).



were nervous. The view of Wilks (764-767) and Greenhow (331) was that the lesion is special and primary in the adrenals, while the symptoms of the disease are due to the secondary effects on the adjacent sympathetic, the solar plexus, and the semilunar ganglion. Modifications of this view were put forward by Alezais and Arnaud (44), Jaccoud (374), and von Kahlden (385). But in many cases of typical Addison's disease no changes in nervous structures could be found, and on the other hand there are numerous examples of irritation of sympathetic ganglia where no symptoms of Addison's disease have occurred.

It may be, however, that the vomiting is of a nervous nature, and due to some effect upon the autonomic nervous system.

The chemical or glandular theory is the one now generally accepted. It is usually subdivided into two : (1) The auto-intoxication theory ; and (2) the theory of internal secretion. According to the latter view, the pathology of Addison's disease is to be explained on the basis of *adrenal inadequacy*—i.e., an interference with the normal internal secretion of the gland. According to the former, the symptoms of Addison's disease are due to the accumulation of poisonous products (*e.g.*, of muscular activity), to remove which it is the duty of the adrenal body. It seems clear that the gland does not effect this removal after the manner of an excretory organ, but there is nothing to prevent our supporting the hypothesis that the secretion of the gland has for its function, or one of its functions, the neutralization of some of the poisonous products of metabolism.

If we admit that one of the functions of the secretion of the gland is to maintain the tone of muscular structures generally, then we have at once an explanation of the extraordinary muscular prostration in Addison's disease. But the effects of adrenin, the secretion of the chromaphil medulla, are practically confined to the muscular structures under the control of the sympathetic nervous system. It may be that the muscular weakness is to be explained on the hypothesis that the adrenals in some way neutralize the poisonous products of muscular activity.

But how are we to explain the pigmentation, the bronzing of the skin, which is, after all, the most striking of all the

symptoms of Addison's disease? Is this symptom related to the colour reactions given by the chromaphil cells of the medulla, and extracts made from them, or is it related to a destruction of red blood-corpuscles which is stated to occur in the central portion of the cortex, or is it due to deficiency in some other function of cortex or medulla?

It seems difficult or impossible to induce pigmentation by experiments upon animals (see, however, pp. 136 and 137).

The pigment is disposed for the most part in places which are exposed to thermal, chemical, and luminous stimuli. From a teleological standpoint the pigmentation might be regarded as a protective arrangement against luminous stimuli [Meirowski (493)], or, according to Bab (60), in discussing melano-sarcoma of the ovary, pigment raises the power of resistance of tissues and organs, and is therefore found in the *locis minoris resistentiæ*. In this view the pigment is a general means of protection against injury. Eiselt (236) comments that this can scarcely hold as a general theory, for pigment becomes developed in large amount in ganglion cells only during the process of degeneration.<sup>1</sup> Wieting and Hamdi (759), discussing melanin-pigmentation, regard the formation of pigment as a protective arrangement—*e.g.*, it is laid down in the skin to protect the underlying structures. Solger (652, 653) looks upon the skin pigment as a protective against ultra-violet light.

The pigments of the body (respiratory, biliary, urinary, melanins, lipochromes, etc.) may be divided into—(1) iron-containing pigments; and (2) fat-containing pigments. The second group includes the degeneration pigments, the lipochromes, and the melanins. The pigment in Addison's disease appears to belong to the melanins.

There are various theories as to the mode of formation of the pigment. It has been suggested that it arises as a result of over-activity of the cells of the stratum Malpighii, due to increased nervous stimulation, the result of mechanical irritation of the nerves round the adrenals. Eiselt (236) believes that in consequence of the failure of the antitoxic adrenal function (of the cortex) the accumulated products

<sup>1</sup> There seems no reason why this pigmentation in degenerating nerve cells should not be an example of a protective effort (albeit ineffective) on the part of the cell.

act autolytically upon the protein. Then, by the action of tyrosinase upon the aromatic molecular complexes thus formed, there arises an accumulation of melanin.

A modification of this theory, but involving the hypothesis that the *medulla* is concerned in the pigmentation, based upon the work of v. Fürth (289, 290) and Halle (346), has been put forward by Adami (24). The melanin appears to be formed by the action of oxidases upon tyrosin and other aromatic products of protein decomposition. It seems possible that adrenin is manufactured in a similar kind of way, so that when the adrenal bodies are diseased the tyrosin and allied bodies accumulate in the tissues, and the greater darkening of the superficial parts most exposed to light and air gains its explanation from the more active oxidation of those aromatic bodies in these regions.

Pathologists have never given due consideration to the essential difference between the cortex and medulla of the adrenals. We have seen that these represent two separate and distinct kinds of tissue, which only come into relation with each other in the higher vertebrates, and bear the relation to each other of "cortex" and "medulla" only in mammals. It is possible that pathology may yet throw some light on the question of the function of the cortex and the question as to a possible physiological relationship between the two constituents of the gland.

#### 7. *Course and Event of the Disease—Diagnosis, Prognosis and Treatment.*

The course of the disease is usually progressive, but the mode of progress is paroxysmal [Greenhow (331)]. All the symptoms are progressive, but not steadily so. The course of the disease on the whole is slow and chronic; but it is subject to alternate exacerbations and remissions. During the remissions strength is to some extent recovered, but after each exacerbation the patient remains upon a lower level than during the previous remission. Greenhow quotes without reference van der Corput, Severini, Löwe and Wolff, and Ringer, all of whom report cases showing the paroxysmal nature of the disease.

In young subjects the disease may run a latent course—that is, the constitutional symptoms first appear suddenly in a fully developed form producing death in a few days.

The diagnosis must depend largely on the extraordinary lack of resistance to fatigue, upon the other constitutional symptoms, and upon the bronzing of the skin. Where this last is absent the diagnosis must be difficult and uncertain.

The prognosis is grave, but the patient may live a considerable time, and care should be exercised in foretelling to what extent life may be prolonged.

The treatment will be dealt with under the therapeutic applications of adrenal substance (p. 208).

#### *8. Other Conditions involving Adrenal Insufficiency.*

Defective development of the adrenals is not infrequently associated with imperfect growth of the brain, particularly in cases of anencephaly and hemicephalo.

Total deficiency of the adrenal medulla is reported by Ulrich (701, 702) and others. Wiesel (758) records a series of cases of what he calls "hypoplasia of the chromaffin system."

#### *9. Excessive Adrenal Function.*

The fact that excessive production and pouring into the circulation of the thyroid secretion appears to lead to a very definite train of symptoms, has naturally suggested the question whether an analogous condition of excessive production of the adrenal secretion may be a factor of consideration in the production of disease.

The most striking effect of the adrenal secretion is a rise of blood-pressure. As pointed out by Adami (25), hyperpiesis, or pronounced and continued rise of blood-pressure, is not an uncommon condition. Roger and Gouget (quoted by Adami without reference) report hypertrophy of the adrenals in a case of experimental arterio-sclerosis induced by lead intoxication, while Vaquez and Aubertin (706), Aubertin and Clunet (56), and Aubertin and Ambard (57), and Pearce (560), and others, have noted a relation between arterio-sclerosis and hypertrophy of the adrenal medulla. Klotz, working in Professor Adami's laboratory, has also reported similar results.

Vasquez and Aubertin put forward three theories to account for the hyperplasia of the adrenal bodies in their cases : (1) The hyperplasia is not the cause of the hypertension at all, but an "antitoxic hyperplasia" due to the effects of the accumulated products of metabolism which possibly also produce the hypertension ; (2) the hyperplasia is the cause of the hypertension, but is secondary to a renal lesion ; (3) the hyperplasia is the cause of the hypertension, and is primary and independent of the kidney mischief.

It is yet too early to state which of these is the correct view. The French writers insist that the adrenal hyperplasia is almost constantly associated with chronic interstitial nephritis. According to Pearce (560), it may equally be associated with chronic parenchymatous nephritis.

On the other hand, Mott (519) states that in his experience in advanced arterio-sclerosis the adrenal medulla is more often atrophied than hypertrophied.

The whole subject is interesting, but is very obscure, and requires further and continued investigation.

#### **E. Extirpation Experiments in Mammals.**

The earliest extirpations of the adrenals were performed by Brown-Séguard in 1856 (140, 141, 143, 144). He employed for extirpation of both glands forty-four rabbits, nine guinea-pigs, two rats, and several dogs and cats. All these animals died in nine to thirty-seven hours after the operation. For the unilateral operation this experimenter used sixteen rabbits, five guinea-pigs, two cats, and two dogs. All these died in twenty-three to thirty-four hours. Later he reported that two dogs survived removal of one gland for eight days. As a rule young animals survived the operation longer than adults. Brown-Séguard came to the conclusion that the death after adrenal extirpation was not due to adventitious lesions connected with the operation, but to a cessation of the function of the glands. He noted marked muscular weakness, but not vomiting or pigmentation, and he supposed that the absence of these two last symptoms is due to the rapidity with which a fatal result supervenes.

These views of Brown-Séguard were vigorously combated by many workers. Gratiolet (330) performed several series

of operations upon guinea-pigs, and came to the conclusion that extirpation of the right adrenal was just as serious as removal of both. This was soon disproved by Brown-Séguard (142), who succeeded in keeping three guinea-pigs out of seven alive for three weeks after right-sided extirpation.

Philipeaux (572, 573, 574) succeeded in keeping white mice and also a certain number of rabbits alive after bilateral extirpation. He concluded that removal of the adrenals does not necessarily lead to death, and that where death ensues this is due to the operative proceedings or some circumstance connected with them, such as peritonitis, and that some animals can survive complete extirpation without showing any symptoms—that, in fact, the adrenals are no more essential to life than is the spleen. This view he firmly maintained, although three of his operated animals died in nine, twenty-three, and thirty-four days.

In order to test the matter further, Brown-Séguard performed a further series of experiments (145, 146, 147) upon rabbits, and felt justified in affirming that the adrenals are more essential to life than are the kidneys, and thought that the survival of occasional animals is due to a vicarious assumption of the adrenal function by the thymus or the thyroid.

Harley (349, 350, 351, 352) employed among other animals the white rat, and found that this animal may indefinitely survive entire removal of the adrenals. From this Harley, as well as Philipeaux and Gratiolet, ascribed the fatal results in other animals to injury to adjacent nerves and bloodvessels.

Among the writers opposed to Brown-Séguard's view may be mentioned Berruti and Perosino (90, 91, 92, 93) in 1857-1863, Chatelain (170) in 1859, Schiff (631, 632) in 1863, Nothnagel (531) in 1879, Burg (152) in 1863, Russo-Giliberti and di Mattei (620) in 1886, Supino (679, 680) in 1892-1893, Pal (548, 549) in 1894, Santi Rindone lo Re (623) in 1895, and Martin-Magron (486).

Among these the observations of Nothnagel deserve special mention. This observer, from clinical observations, thought that a chronic inflammation of the adrenals would be more likely to induce symptoms resembling those of

Addison's disease than removal of the glands. Accordingly he resorted to the method of crushing the bodies. He operated upon 153 rabbits, and found that if the operation were performed upon the two sides with an interval of three or four weeks between, then the animals survived and showed no serious symptoms. Among the 153 bilaterally operated rabbits, Nothnagel observed in three cases pigment spots on the mucous membrane of the mouth. These were noticeable one, three, and five months after the second operation. The author did not, however, attach any particular importance to them. He thought, indeed, that the disease of the adrenal glands had no immediate relation to pigmentation.

The statement that removal of both adrenal bodies does not necessarily lead to death was denied by Tizzoni (692-695). This author came to the conclusion that in rabbits the destruction of one or both of the adrenals results in death if sufficient time be allowed to elapse. He obtained similar results with dogs.

The opinion that unilateral extirpation could lead to death was strenuously opposed by Stilling (665), who found that young rabbits from which one adrenal had been removed could develop quite normally, and live more than a year without showing any untoward symptoms. In thirty cases investigated Tizzoni found pigmentary changes in thirteen. These came on at the earliest two months after the operation, and occurred exclusively in the mucous membrane of the nose and mouth. They were of the same character as those found in Addison's disease.<sup>1</sup> Stilling was unable to confirm these results. Tizzoni considered that death, which might occur after removal of one capsule, was due to lesions of the nervous system.

Abelous and Langlois (14, 16) employed various means for experimental lesions upon the adrenals, such as ligature, crushing, and cauterization, but most frequently the last method was used. They report that after complete destruction of one gland some animals suffered a loss of weight and a small proportion died. After complete destruction

<sup>1</sup> Königstein (403) has more recently reported that in five out of nine dogs he has observed a distinct darkening of the stain after adrenal extirpation and some hours' application of heat by means of a warm chamber. See, however, Meirovski (494).

of both adrenals the animals soon died as a rule. The duration of life could be increased by performing the operation at two sittings with an interval of several days between them. After destruction of a fifth part of each gland, with an interval of one or two days between the two operations, the animals could be kept alive, but there was considerable emaciation. If an interval of eight to fifteen days were allowed to elapse between the two operations, then the animals lived without symptoms. If the half of each organ were cauterized away, the animals rapidly wasted away and died, but not so quickly as after total destruction. The animals employed in the experiments were guinea-pigs.

Langlois (437, 438) obtained similar results with other kinds of animal.

Alezais and Arnaud (40, 41, 42, 43), in a series of papers entitled "Recherches Expérimentales et Critiques sur la Toxicité de la Substance des Capsules Surrénales," give an interesting account of the history of the subject, and conclude that the suprarenal capsule, though still functioning in the adult, is not indispensable for life. Its unknown functions may be disturbed without any other results than a hyperpigmentation of skin and mucous membranes. But a lesion of the glands frequently induces death by affection of the nervous system. The pigmentation was confined to the mouth and nostrils, and the authors do not appear to be convinced that it was not accidental and independent of the lesion of the adrenals.

In 1892 Thiroloix (690, 691) reported that dogs died in twenty-five to forty hours after total extirpation of both adrenals.

Dominicis (215) obtained uniformly fatal results, but his work was of a very unreliable character.

Szymonowicz (683) found that his dogs died in fifteen hours after the double operation,<sup>1</sup> while Kudinzew (428) reports death in eighteen to twenty-four hours.

Pigmentation of the skin has been recorded by F. and S. Marino-Zucco (483) after inoculating the adrenals of rabbits with "pseudo-tubercle" bacillus.

Boinet (120-124) obtained some interesting results, which

<sup>1</sup> See, however, the criticism of Hultgren and Andersson (369).



however, have not been confirmed. After damage to the adrenals in rats, he records an accumulation of dark pigment in several tissues and organs, and feels justified, therefore, in referring to an "experimental Addison's disease." He notes, also, a diminution of resistance of the decapsulated rats to the toxic action of different substances.

Hultgren and Andersson (369) in 1899 published the results of a carefully conducted series of extirpation experiments upon rabbits, cats, and dogs. The effect varied very considerably in different animals.

In cats the unilateral operation (extirpation of one adrenal) never induced death, but, especially in old cats, there was some temporary disturbance of the general bodily health. Bilateral extirpation in these animals, whether carried out at one, two, or three sittings, led to death, without exception, in a few days. The average duration of survival after extirpation of both adrenals at one operation was 68 hours (nine cases); at two operations, 134 hours (eleven cases); at three operations, 88 hours (five cases), but in the last instance there were three cases of infection.

Extirpation of one and amputation of the other gland<sup>1</sup> in one sitting was generally very badly borne. Of the nine cats operated on in this fashion, only two survived any considerable time; one died in six hours, probably from the effects of the anæsthetic, and three in thirty to seventy-two hours. In these last the adrenal left behind had undergone necrosis. The three remaining animals died from various diseases within three weeks after the operation. It appears from these experiments that the removal of a large part of the adrenal tissue renders the animal more susceptible to infection.

Extirpation and amputation carried out at two sittings is less dangerous; out of thirteen animals so treated, two died from the actual operation, and three from necrosis of the adrenal left behind. The remaining eight all lived more than seven days, and of them two died of intercurrent diseases. If the removal of the glands be carried out at several operations, the length of time which elapses between the operations makes no difference to the result.

<sup>1</sup> In these "amputation" experiments a small portion only of one gland was left behind.

Hultgren and Andersson came to the conclusion that the resistance of castrated animals to adrenal extirpation is generally greater than that of normal animals. While, for example, normal animals survived complete extirpation at one operation for 61 hours, the corresponding time for castrated animals was 121 hours. In this relation the authors call attention to the striking morphological resemblance between the cells of the adrenal cortex and the interstitial cells of the testis and ovary.

In rabbits total extirpation of both glands at one operation is always fatal, and death occurs on the fourth or fifth day. If the operation is carried out at two sittings, the duration of life is considerably increased; and three rabbits in which there was an interval of nine to fourteen days between the two operations lived 121 to 125 days, and were then, in perfect health, killed.

After extirpation of one and amputation of the other gland most of the rabbits lived a long time—as long as 320 days. The authors, immediately after stating this result, say: “Dieses Ueberleben der totalen Entfernung der Nebennieren beim Kaninchen is durchaus nicht durch die Anwesenheit wenigstens makroskopisch nachweisbarer accessorischer Nebennieren bedingt.” Now, these cases were not cases of total removal of the adrenals, for some tissue of the amputated gland was always left behind. But perhaps this is meant to refer to the three cases of the previous paragraph, where the operation was performed in two sittings with an interval of nine to fourteen days between them. But apparently these were not cases of complete removal, for the gland was transplanted into the musculature.

Unilateral extirpation in rabbits produces no ill-effects, and the same applies to dogs. Hultgren and Andersson only performed one total extirpation upon a dog, which lived six days.

According to Hultgren and Andersson, the symptoms after removal of the adrenals are very characteristic. After the operation the animal recovers in a few hours, and in the first few days shows no ill-effects from the operation, except some loss of appetite. During the last twenty-four hours before death, or earlier, the animal becomes

stupid and quiet, and shows (especially is this the case with cats) weakness and uncertainty of movement in the hinder extremities. During this period, too, the temperature begins to fall, and the apathy and weakness increase. Then the hind-limbs become stiff, the animals tire on the slightest exertion, and show extreme prostration. Finally, with increasing asthenia, there is dyspnoea, heart-weakness, and death. In rabbits convulsions are common, but do not occur in cats and dogs. The authors lay considerable stress upon the loss of weight which occurs even after the unilateral operation.<sup>1</sup> This symptom is less marked if the operation be carried out upon castrated animals. Fall of temperature, too, is regarded by them as a significant symptom. They could detect no change in the hæmoglobin of the blood, nor in the number of red and white corpuscles. They could detect no change in the electrical excitability of the nerves, and deny that removal of the adrenals gives rise to symptoms resembling those of poisoning by curare. There was no true paralysis, but only weakness and prostration. As pointed out by Albanese (33, 34), the operated animals are very sensitive to bodily movements. Adrenal extirpation has no effect on the protein metabolism. This applies, at any rate, to rabbits and cats. The Scandinavian authors consider it very probable that the adrenals have a varying functional significance in different classes of animals.<sup>2</sup>

Strehl and Weiss (678) operated upon 114 animals, and found that total extirpation always causes death in from four hours to five days. If the operation was performed at two sittings, the second gland was always found to be enlarged. Among the symptoms noted after extirpation by these writers are muscular weakness, a low temperature, and a low blood-pressure. After extirpation of one gland in rabbits, cutting or clamping the veins of the second acts exactly like extirpation. On removal of the clip, the blood-pressure rises at first above the original height. The gland, therefore, normally gives to the blood a substance which serves to maintain the normal blood-pressure. Injection of

<sup>1</sup> This result was also obtained by Elliott and Tuckett (239), and has been frequently observed by the present writer in the experiments of Gardner and Mothersill.

<sup>2</sup> This is probably true of all the "ductless glands."

adrenal extracts prolongs the life of the operated animals, and the blood-pressure rises considerably.<sup>1</sup>

Strehl and Weiss give the following tabular statement of their results :

Species of Animal.	Duration of Survival in Hours.	Number of Animals.
Dogs .. .. .	22—75	7
Dogs .. .. .	75—138	3
Cats .. .. .	15—28	15
Cats .. .. .	28—47	2
Rabbits .. .. .	8—14	26
Guinea-pigs .. .. .	4—9	20
Rats .. .. .	15—19	4
Mice .. .. .	8—13	10
Hedgehog .. .. .	14	1
Weasel .. .. .	21	1
Frogs .. .. .	22—45	25

Krichtpenko (426) found that the adrenals are not essential to the life of the rabbit. According to this author, other organs can take on the functions of the adrenals after their removal.

Biedl (105) performed a series of experiments upon dogs, cats, and rabbits. These were carried out by a new method. In a preliminary operation by a lumbar incision the glands were “dislocated,” the vascular connections were not severed, and the glands were stitched into their new position between the skin of the back and the dorsal musculature, so that they remained in a living condition and easily accessible extraperitoneally. After three or four days the glands were exposed by a skin incision, the vessels tied, and thus could extirpation be performed in the easiest possible manner.

It was found that extirpation of one gland produced no serious effects, but that after extirpation of both adrenals the animals died, almost without exception, in two to four days. Two rabbits which survived sixteen and twenty-eight days respectively were found to possess accessory adrenals on the vena cava beneath the renal veins.

As we have seen, Boinet (120-124) succeeded in keeping rats alive for a considerable time after double epinephrectomy ; and Harley (349-352) many years ago found the rat

<sup>1</sup> These experiments on blood-pressure will be referred to again.

is able to withstand removal of both adrenal bodies. According to Wiesel (748, 749, 750), this is due to the fact that the rat normally possesses between the testis and epididymis accessory adrenals which are found to undergo compensatory hypertrophy after extirpation of the chief organs. These accessory bodies consist entirely of cortex.

In guinea-pigs a compensatory hypertrophy of accessory cortical bodies can be shown to occur [Velich (712)], but this is never sufficient to keep the animal alive after complete removal of the main glands.

The case of the rat and the results of extirpation experiments upon this animal seem to point strongly towards the cortex being the part of the adrenal body which is essential to life. We shall, however, have to return to this subject again.

We see, then, that later work has confirmed in a general way the statements of Brown-Séguard as to the necessity for life of the adrenals. We cannot, however, altogether disregard the very considerable number of exceptions which have been recorded by various observers. Moore and Purinton (514, 515) report the survival of a goat for twenty-two days after complete removal of both adrenal glands, and they state that no accessory bodies could be detected.

According to Mayer (491, 492), the diabetic puncture is ineffectual in animals from which the adrenals have been removed. Further, in such animals the glycosuria resulting from extirpation of the pancreas is much reduced. Frouin (277) states that the pancreatic diabetes is also much reduced in severity in animals from which one adrenal and two-thirds of the other have been previously removed. This matter will be referred to again in connection with the subject of adrenal glycosuria.

Levin (456) reports that the blood of animals deprived of adrenals, when injected into another animal, raises its blood-pressure, but the tracing he gives indicates that the rise is not considerable. He hints that the substance which has this action may be something of a different nature from adrenin.<sup>1</sup>

<sup>1</sup> According to Gautrelet and Thomas (296), after extirpation of the adrenals in dogs the heart contraction becomes weak, and the rhythm quicker, while the blood-pressure sinks after five hours to 6 centimetres Hg and later to 1 centimetre. The same authors (297) report that in decapsulated dogs

#### F. The Question as to Accessory Adrenal Bodies in Relation to Extirpation Experiments upon Mammals.

It will be seen, from a perusal of the section on the comparative anatomy of the adrenal glands, that not only accessory adrenals consisting of both portions of the organ may be present, but that there may also be some glandules consisting of cortex only. The presence of chromophil bodies and cells in different regions must also be borne in mind (see Fig. 36). How far does the existence of these various bodies explain the discrepancies between the results obtained by different observers after adrenal extirpation? We know that some of the larger masses of chromophil tissue (such as the parasomata of Zuckerkandl and the abdominal chromophil bodies in various animals) contain adrenin [Biedl and Wiesel (108); Vincent (731)], and this may have the same physiological purpose as that manufactured by the adrenal medulla.

Schäfer (626) recently exhibited a white rat operated upon by Harley some time between 1856 and 1858. This rat had the spleen and adrenals extirpated when it was only a month old and quite small. It increased in size after the operation quite as fast as its fellows which had not been touched. The animal was killed when five months old, and no discoloration of the skin or hair could be detected. The lumbar and other lymphatic glands were found enlarged.<sup>1</sup> Commenting upon this, Professor Schäfer says: "The rat happens to be the one common animal which is able to withstand complete removal of both suprarenal capsules. The reason for this was not at the time apparent, although it is now known, for the rat is exceptional in possessing in various parts of the back of the abdomen and pelvis numerous small glandular structures which are composed of cells having the same characteristic features and functions as the cells of the suprarenal medulla."

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excitation of the splanchnic no longer induces glycosuria, as it does in normal animals. They further report (298) that dogs and rabbits, after adrenal extirpation, become poikilothermic in that their body temperature, within certain limits, follows that of the external air, and that there is reduction of the excitability of the sympathetic (299).

<sup>1</sup> This description is taken from the catalogue of the museum of University College Hospital, whence the specimen was borrowed by Professor Schäfer for the purpose of his lecture.

But all observers have not been successful in keeping rats alive after double adrenal extirpation. Thus, H. and A. Cristiani (195) found that in their experiments, unless a little of the medullary substance were left behind, the rats always died. From these experiments we should be justified in concluding that it is the chromaphil tissue (including the medulla of the adrenal body) which is essential to life. But, as we have already seen, Wiesel (748, 749, 750) arrived at a different conclusion—viz., that it is the survival of accessory cortical substance which saves the animal's life. We thus see that the experimental evidence as to the effects of extirpation of the adrenals in the rat is somewhat conflicting, and the explanations offered by different observers as to the occasional or frequent absence of ill-effects after extirpation are also conflicting. Moreover, it does not appear to be the case that the rat is more richly endowed with extracapsular chromaphil cells than are other common animals. The present writer has been so far totally unable to demonstrate any such tissue by the method of Stilling and Kohn, and is further informed by Dr. Kohn that there is, at any rate, no essential difference between the rat and other animals as regards its chromaphil tissues.

Vassale (707, 708), who has performed a series of experiments with full knowledge of the anatomy of the chromaphil cells and their distribution in different animals, points out that the "paraganglion abdominale aorticum" is the most important mass of chromaphil tissue outside the adrenal body, and that it is always present, though in varying degree in the animals ordinarily used for experiment (dog, cat, and rabbit). The removal of one adrenal and the abdominal chromaphil body causes death in young cats with the same symptoms as those obtained after bilateral extirpation of medulla only. Vassale thinks that survival of animals, when it occurs after extirpation experiments, can be satisfactorily explained by the extra amount of extra-adrenal chromaphil substance which happens to be present in these individuals.

A further discussion of the question as to the relative importance to life of the cortical substance and the chromaphil material can only be carried on after the account of extirpation experiments upon lower vertebrate animals.

According to Biedl (105), the cortical accessory adrenals occur very rarely in dogs and cats, in rabbits in about 15 to 20 per cent. of animals examined, in rats in almost 50 per cent. of cases, in guinea-pigs not more than 4 per cent. of cases.

#### G. Extirpation of the Adrenals in the Lower Vertebrata.

Perhaps the best-known and most often quoted series of extirpation experiments upon any animal is that carried out upon frogs by Abelous and Langlois (12, 13, 15) in 1892. This was, of course, at a period before the discovery of the physiological effects of adrenal extracts upon the blood-pressure. The authors employed frogs because these animals, they say, do not suffer from the shock of operations as do mammals, and, in general, tolerate operative proceedings very well. Abelous and Langlois were the first to study the physiology of the adrenals in the frog. They remark upon the paucity of exact knowledge of the structure of the organs.<sup>1</sup>

Destruction by means of the actual cautery was the method of extirpation employed by Abelous and Langlois. A platinum wire brought to a red heat was applied to the bodies on the anterior surface of the kidneys. The authors found that male frogs are more suitable for the operation than female, and summer frogs better than winter frogs. There was never any post-operative shock.

Total destruction of both capsules always led to death. Immediately after the operation the animals were normal. It was only after a certain period that one observed ill-effects which finally caused death. The duration of survival was variable. It varied according to the season; winter frogs might live twelve or thirteen days, but summer frogs never longer than forty-eight hours. On the other hand, if the winter frogs were kept at a mean temperature of 22° C., their period of survival was much diminished, and from twelve to thirteen days it was reduced to three.

The symptoms which followed destruction of both capsules consisted essentially in a progressive paralysis beginning in the hind-limbs, then becoming general and inducing

<sup>1</sup> Abelous and Langlois quote only Ecker (231), but they might have found a much better account in Eberth's article in Stricker's "Handbuch" (229).



death. On the day of the operation the animal remained well. It was as a rule at the end of the twenty-fourth to the thirtieth hour that symptoms came on. First one noticed a distinct inco-ordination in the movements of the hind-limbs when the frog jumped. Also the animals quickly became fatigued, and asthenia became more pronounced. This paresis affected first the flexors and adductors, and finally the extensors; the frog was finally no longer able to respond even to the strongest stimulations except by way of the feeblest movements. Then the fore-limbs became affected, and the animal was completely inert. The respiration became slower and slower, and with contracted pupil the animal died.

If the animal were stimulated from time to time so as to provoke movements, it was found that the paralysis came on much more quickly, and the duration of survival was considerably shortened. From these facts the authors concluded that the length of survival was in inverse ratio to the chemical changes going on in the body. The more active these changes—as, *e.g.*, in summer frogs—the more quickly did death supervene.

Destruction of one capsule never induced death. The animals after such an operation showed no untoward symptoms, and their attitude and reactions were perfectly normal. Complete destruction of one capsule and destruction of the greater part of the other generally led to death, but the survival was always longer than after complete destruction of both. If the fragment left behind were of any considerable size, the survival was as long as in the animals in which only one gland had been destroyed. The insertion under the skin, in the dorsal lymph sac, of some fragments of kidney with the adrenals attached taken from a normal frog, prolonged the survival. Animals so treated might live twice as long as animals not so treated. The authors record that summer frogs were by this means enabled to live five or six days. Post mortem it was found that the grafted capsules had disappeared—*i.e.*, the graft did not succeed. Injection of a saline extract of healthy glands only prolonged the survival by about twenty-four hours.

Now we come to some observations by Abelous and Langlois upon which they themselves laid considerable stress,

and which have played a prominent part in all subsequent discussions on the functions of the adrenal bodies. They found that intravenous or subcutaneous injection of the blood of a frog dying after extirpation into a frog recently operated upon induced rapid paralysis and death. The same injection into a normal frog only produces slight temporary symptoms. The authors were convinced that death after extirpation of both capsules is in reality due to the suppression of essential organs, and not simply the result of the shock of the operation. They further proved that the effects were not due to injury to the kidney. Their theory was that death resulted from the accumulation in the blood of one or several toxic substances of unknown nature, and that the suprarenal capsules are capable of the elaboration of a substance which neutralizes the toxic effects of such substances. The toxic symptoms were stated to be those of curare-poisoning—paralysis, that is to say, of the connections between nerve and muscle.

These observations were in the main confirmed by Gourfein (327, 328, 329), who, however, could not ascertain that there was any difference between winter and summer frogs as regards the results of extirpation, and who denied also that the blood of operated frogs, when injected into other frogs, gives rise to symptoms like those of curare-poisoning.

The same author also carried out a series of observations on pigeons and tritons. The pigeons only survived four to twenty-four hours if total extirpation had been performed; if only one-eighth to one-tenth of the organ remained behind, the animals lived fifteen days. Unilateral extirpation in tritons produced no symptoms. If only a speck of one adrenal remained behind, this was sufficient to keep the animal alive for from eighteen days to nine weeks.

Pettit (567, 568, 569) was apparently the first to operate upon fishes. He performed a series of experiments upon the eel, having chosen this animal because it is one of those rare Teleosts which has its adrenals placed on the ventral surface of the kidneys. He did not, however, perform any total extirpations, since he was only interested in noticing a compensatory hypertrophy of one gland after removal of the other. This, he says, indicates a secreting function for the adrenal of the eel. Pettit looks upon this organ in the

eel as the fundamental type of the suprarenal capsule, but he was apparently unaware that it consisted only of cortical substance.

Since the corpuscles of Stannius contained no chromophil tissue, the Teleostean fishes appeared to offer an admirable opportunity of testing how far the cortical adrenal glands were essential to the life of the animal. Accordingly a series of experiments were performed by the present writer in 1898 upon eels (724). The results showed that an eel will survive the operation for a long time. The conclusion drawn was that the cortex of the adrenal is not essential to the life of the animal, but the discovery by Giacomini of the cranial cortical adrenal in Teleosts renders such a conclusion unwarrantable (see p. 102).

Biedl's experiments upon Elasmobranch fishes will be referred to in the following section.

#### **H. The Question as to the Relative Importance to Life of Cortex and Medulla.**

We have seen that the extirpation experiments upon mammals have not definitely determined the question as to which constituent of the adrenal is essential to life, or whether, indeed, it is to the suppression of the compound organ in its entirety that we must attribute death after extirpation. We have seen that Bittorf (112) believes there is no special part of the organ which is of supreme importance in the pathology of Addison's disease. He considers that the adrenal bodies are single organs clearly essential to life, interference with which causes definite ill-results (see pp. 128 and 129). H. and A. Cristiani and Vassale, as we have seen, concluded from experiments upon mammals that the medulla is the vitally essential constituent, while Wiesel came to the conclusion that the cortex is the part essential to life.

Biedl (103) states that in mammals he has succeeded in removing the cortex, leaving the medulla behind intact, and that the operation was followed by the death of the animals. So he concludes that it is the cortex which is essential to life. With regard to this experiment one must agree with the comment of Schäfer (626), who says: "But I think the experience of most people will lead them to believe such a separation to be impossible." Moreover, it

would seem certain that, even if the immediate surgical difficulties could be overcome, the damage to the remaining medullary substance and interference with its blood-supply would be such as to render it functionless and lead to atrophy. Moreover, Vassale (708), in attempting the same experiment, obtained opposite results.

Ciaccio (172, 173, 174, 176, 178) believes that the medulla is the portion of the gland which is essential for life.

Biedl (103) says that he has succeeded in determining for the inter-renal of Elasmobranchs that after its extirpation the animals can live two or three weeks, and then die with symptoms of general prostration, just as do mammals after extirpation of both dual adrenals. Again, he concludes that the cortex is the essential part. These experiments upon Elasmobranchs must be very difficult, but so far they certainly seem to point to the cortex as the vitally essential tissue.<sup>1</sup>

Although it would be unwise to attempt to pronounce definitely upon the point, it would seem, in the opinion of the present writer, that the balance of evidence at the present time is somewhat in favour of the view that the cortex of the adrenal is of greater vital importance than the medulla.

### I. Changes found Post Mortem after Extirpation of the Adrenals.

Reference has already been made to pigmentary changes after double extirpation. These were recorded by Tizzoni, Nothnagel, and Boinet.

Tizzoni (692, 693, 694, 695) reported severe lesions in the central and peripheral nervous system. He describes also extensive destruction of nerve fibres and ganglion cells, with marked congestion, alterations in the vessel walls, and hæmorrhages and leucocytal infiltration in all parts of the nervous system. But Tizzoni's work in this respect must be cautiously considered, for it must be remembered that he records death after removal of *one or both adrenals*, and this is opposed to the experience of every subsequent investigator.

Poll (582, 583, 585) found in some cases among his rats

<sup>1</sup> The validity of these experiments is, of course, based upon the assumption that there is in Elasmobranchs nothing corresponding to the cranial cortical body discovered by Giacomini in Teleosts.

after unilateral removal and transplantation numerous reddish-black spots on the skin, but never on the mucous membranes.

Hyperæmia and hæmorrhages of the lungs have been observed after both the bilateral and the unilateral operation. Changes in other organs have only been noted by a few observers. Donetti (217) states that he found changes in the nerve cells of the central nervous system of guinea-pigs and rabbits, especially in the medulla oblongata. The nuclei of the cells became vesicular, eccentric, and granular, and might disappear. He also noted changes in the nerve-cell body.

Marengi (482) found that in animals which survived adrenal extirpation for a long time there were mitoses in the glandular portion of the pituitary body.

Moore and Purinton (514) record cardiac thrombosis following complete removal of the adrenals. The presence of ante-mortem clots in the heart has been observed on numerous occasions after adrenal extirpations in the laboratory of the present writer.

#### **J. Compensatory Hypertrophy of the Adrenals.**

Numerous authors have described a compensatory hypertrophy of one adrenal after the removal of the other. Thus, Stilling (666) found in rabbits, after extirpation of one adrenal, a considerable increase in weight of the one which was left behind. Pettit (567, 568, 569) describes a similar hypertrophy in the cortical adrenal ("corpuscle of Stan-nius") in the eel, after the removal of the glandule of the opposite side. Simmonds (650) states that in young rabbits and guinea-pigs, after extirpation of one adrenal, the other may hypertrophy—in rabbits to twenty to eighty times, and in guinea-pigs to 160 to 180 times its original size!

But all observers could not record such hypertrophy. It is probable that there is a difference in this respect between different species. Harley among the older workers, and Poll among the more recent, could not observe any such hypertrophy in rats. There can be no doubt whatever that such a compensatory hypertrophy may be regularly and easily observed in the dog.

The compensatory hypertrophy of accessory adrenals in

the rat, which is described by Wiesel, has already been discussed. This may be related to the absence of hypertrophy on the part of the chief organ. A similar hypertrophy of the accessory adrenals which are found along the walls of the vena cava of the guinea-pig has been described by Velich (712).

According to some observers, the chromaphil cells, whether of the adrenal medulla or of the extra-medullary corpuscles, seem to be incapable of hyperplasia. If this really be the case, it is interesting to compare the fact with another to be referred to again later—viz., that in grafting experiments it is only the cortex which “takes”; the medulla disappears. It is possible that this lack of power of growth and of resistance to absorption is related to the high degree of specialization of the chromaphil tissues [Vassale (708)].

That the functional capacity of one adrenal left after the removal of its fellow is not increased is the conclusion drawn after some experiments by Battelli and Ornstein (81). These authors removed one adrenal from dogs and rabbits, and let them live for from two to seventeen days. After this period the adrenalin contents of the remaining gland were estimated by Battelli's colorimetric method (77) in order to obtain a measure of the degree of vicarious function. No increase in the adrenalin of the remaining gland, but rather a decrease, was found. These experiments, of course, have no bearing on the cortex of the organ, but only on the chromaphil medulla.

Elliott and Tuckett (239) could not readily produce compensatory hypertrophy. They found that the English guinea-pig cannot survive the removal in one operation of a single gland. By piecemeal extirpation a gland was successfully removed; the medulla of the gland left behind grew, and the cortex apparently not. But in a rabbit both cortex and medulla grew. This does not accord with the observations of Poll and Vassale. From some experiments of Drs. Gardner and Mothersill now being carried out in the University of Manitoba, the results of which have not yet been published, the present writer is inclined to believe that in dogs, after a large part of the adrenals have been extirpated, there is a notable compensatory hypertrophy of the abdominal chromaphil body.

### K. Transplantation of the Adrenals.

Although considerable attention has been devoted to the subject of transplantation of the thyroid, comparatively little has been done in this direction with the adrenal bodies.

Canalis (157) appears to be the earliest worker who attempted adrenal transplantation. He grafted small portions of the adrenal into the kidney, but they became necrotic and were absorbed. Only once, fifteen days after the operation, did he find in the kidney scar the capsule of the adrenal and some of the cells of the external layer of the cortex.

Abelous (11) was the first to experiment with frogs. He could not be sure whether the grafted organ atrophied or not.

Boinet (120) transplanted adrenals intraperitoneally into rats. He observed atrophy and absorption, which, however, was sometimes delayed. He noted red spots on the transplanted organs, which he called "hémorragies capsulaires."

Gourfein (329) reports that six days after the transplantation of frog's adrenal into the lymph sac of another frog the organ became decolorized, and attached by connective tissue to the muscles. After twenty days the decolorization and adhesions were more marked, and after forty days the gland was absorbed. When the adrenals of a guinea-pig were transplanted into the lymph sac of a frog there were adhesions, leucocytal infiltration of the gland, and inflammation of the surrounding tissue.

De Dominicis (216), who worked with dogs, changed the position of an adrenal, but did not altogether destroy the connections with surrounding parts. After ten to fifteen days there were no changes in the gland cells.

Jaboulay (373) on two occasions transplanted the adrenals of a dog into a patient suffering from Addison's disease. The fate of the adrenals is not recorded. The patient died in twenty-four hours.

In all these experiments the effect was no more than that of the administration of a certain amount of adrenal substance in the form of the gland itself. The effects, if any, were purely chemical.

Poll (582, 583, 585) was the first to make a systematic macroscopic and microscopic investigation of the transplanted gland. This author employed rats for his experiments. He removed the left adrenal body from behind, and in one series of experiments transplanted it into the dorsal muscles, in another series beneath the skin of the back. In addition to some changes in the elements of the capsule, Poll records that the cells of the zona glomerulosa and the outer part of the zona fasciculata became changed into large polyhedral, at times pigmented, structures, which degenerated with the formation of fat droplets and pigment granules. The cells of the inner part of the zona fasciculata, the zona reticularis, and the medulla degenerate within the first week, forming a necrotic focus in the centre of the adrenal. This is absorbed in the course of the second week, and in connection with the process of absorption giant cells arise from the altered cells of the outer part of the gland. These finally disappear. Into the centre of the adrenal, at the place where the suprarenal vein leaves the gland, a band of connective tissue grows and develops, and remains permanently. In the course of the third week heaps of cells occur in the capsule, which resemble cortical cells, but possess only small compact cell bodies. These heaps fuse together, and grow into large masses having the form of a segment of a sphere. In these masses the small cells show signs of an arrangement like that of the zona fasciculata. In the interior, progressing outwards, begins a transformation of these cells into clear, finely reticular elements in all respects like cortical cells. Intramuscular implantation gives about twice as many successful results as subcutaneous. Favourable results were obtained only with young, small, and middle-aged animals.

V. Schmieden (634, 635) reports that he has succeeded in grafting fresh slices of rabbit's adrenals into the same animal from which the tissue was taken.

H. and A. Cristiani (195) and Stilling (670) have also transplanted adrenals, and in many respects the results obtained by these authors agree with those of Poll described above. Stilling transplanted adrenals into the testis, and found typical cortical substance as long as three years after the operation.



It seems, then, that in all cases where the adrenals are transplanted the medulla disappears. This fact is, perhaps, not without significance as bearing upon the morphological relationship existing between the two constituents of the gland. The results of transplantation experiments are also of considerable importance in view of any future attempts to replace the adrenal function either in the human subject in Addison's disease or experimentally upon animals after extirpation of the organ.<sup>1</sup>

### L. The Pharmacodynamics of Extracts of Adrenal Medulla (Chromaphil Tissues) and of Adrenin.

#### 1. *The General Physiological Effects of Chromaphil Tissue Extracts and of Adrenin.*

It has already been noted in connection with the account of extirpation experiments that a few observers have obtained beneficial results after removal of the gland from administration of adrenal substance either in the form of the gland itself (grafts) or as watery or saline extracts [Strehl and Weiss (678), Abelous and Langlois (12, 13, 15)].

In the present section we have to deal with the effects produced by the administration of the active principle to the normal animal. In the first instance we shall confine ourselves to the general effects (toxic) produced upon the animal as a whole, reserving the special effects upon different systems—*e.g.*, the hæmodynamics—for a subsequent section.

The earliest important investigations upon the effects of injecting adrenal extracts into animals are those of Foà and Pellacani (263, 561). In their earlier experiments these observers employed aqueous solutions of fresh animal substances, including the adrenal body. They succeeded in causing death in a dog by injecting subcutaneously

<sup>1</sup> Numerous experiments upon transplantation of different organs and tissues have shown that as a general rule the transplanted portions degenerate in a few months, even if they have made connection with surrounding tissues, and have undergone some temporary growth. Among the exceptions are portions of skin, thyroids, adrenals, and the notable case of Ribbert (603), who succeeded in grafting the Anlage of the mammary gland of a young guinea-pig upon the outside of the ear. The gland not only developed but ultimately secreted.

For the literature of transplantation in general see v. Recklinghausen (600), Marchand (480), Aschoff (52), and Stilling (671).

the adrenals of a calf in the form of neutral extract. Similar but more rapidly fatal effects were obtained in experimenting upon guinea-pigs and rabbits, but when injected intravenously they obtained like results from extracts of liver and kidney. So they concluded that the effect was not a specific one.

In their later work, produced conjointly (562, 563), Foà and Pellacani, eliminating the injurious effects of fibrin ferment in their extracts, found that the toxic action was specific for the adrenals. They further determined that the toxicity is not due to the acids present, for if one separates these out the extracts remain active. Further, the toxic effects are not due to a ptomaine which the authors found in the glands, for this is physiologically inactive. They conclude that the active principle of the adrenals paralyzes the spinal cord and the medulla oblongata, destroys completely all motion and sensation, and kills by paralysis of the respiratory centre. These authors prepared their extracts by boiling, evaporating to dryness, extracting in the cold with alcohol, and redissolving in water. "After filtering and evaporating the aqueous solution, one obtains a residue coloured black, of a peculiar odour, of very acid reaction, and which, in a dose of 1 gramme, kills a healthy dog." Thus it will be seen that the doses employed corresponded to very large quantities of the fresh gland substance.

These experiments were adversely criticized by Alexander (38), who suggested, with considerable justice, that chemical changes might have taken place in the active principle during the complicated manipulations employed by the Italian observers. Alexander even considered that the results they obtained were of no physiological importance. Mattei (489) also was of a similar opinion. F. and S. Marino-Zucco (484), Marino-Zucco and Dutto (485), and Guarnieri and Marino-Zucco (338), concluded that the effects observed were due to neurin, while Jacowicki and Armin Kohler (377) suggested that the symptoms were those of putrid intoxication.

Alezais and Arnand (40, 41, 42, 43) came to the conclusion that in all probability in the substance of the adrenal bodies in the fresh state there is not any toxic principle. This, they consider, only becomes developed under the influence

of certain conditions, among which are the manipulation employed in the preparation of the extracts. They do not, however, pronounce finally on the subject.

Oliver and Schäfer (537, 538, 539) injected subcutaneously comparatively large doses of aqueous adrenal extracts into the dog, the guinea-pig, and the cat without obtaining any very obvious effects. But in the rabbit a large dose of adrenal extract administered subcutaneously invariably produced death. Among the symptoms noted was a very low temperature. In frogs the symptoms were those of paralysis due to the action of the poison upon the central nervous system. Large doses were recovered from in a comparatively short time.

Cybulski (200, 201) discredits the toxic effects of adrenal extracts in the case of rabbits, in spite of their invariably fatal results. These he considers to be due to an effect principally upon the vasomotor centre.

Gourfein (327, 328) determines that in treating watery extracts with strong alcohol one obtains a precipitate of "albuminoids which, redissolved in water, are deprived of toxic properties, while the substances which have remained dissolved in the alcohol present, on the contrary, a very powerful toxic action, and are not destroyed by heat."

Gluzinsky (319), injecting intravenously, obtained paralysis of the posterior part of the body, and convulsions in the anterior part, with acceleration of the respiration and dilatation of the pupil. The animal succumbed amid progressive dyspnoea and general paralysis.

Dubois (224, 226) attempts to account for the variations in the effects obtained by classifying them under three heads: (1) Those depending upon the animal experimented upon; (2) those due to the animals from whose glands the extracts were made; and (3) variations conditioned by the mode of obtaining the extracts. He found that fatigue previous to injection rendered the animal much more susceptible to the toxic action, that extracts obtained from the glands of wild animals were more powerful than those obtained from animals which had been kept in captivity, and that the medullary region was much richer in the active poison than the cortex.

The present writer (726, 727) in 1897-98 performed

a series of experiments upon rabbits, guinea-pigs, rats, mice, frogs, toads, as well as upon dogs and cats. The fresh-chopped glands were boiled with normal saline solution, and the extract filtered, or the fresh glands were pounded with water or normal salt solution and sand in a mortar, and the filtrate injected without boiling. Dried material was also sometimes employed for the preparation of the extracts. Sometimes cortex and medulla were carefully separated, and separately used for extracting and injecting, either by the fresh or the dry method. In addition to the above, glycerin and alcoholic extracts were employed.

In most of the experiments the injection was made subcutaneously beneath the skin of the back with a hypodermic needle. In some cases the extract was injected into the pleura or the peritoneum, and in a few cases into a vein. Numerous control experiments were performed.

The adrenals employed in the making of the extracts were obtained mostly from the sheep, but some were taken from the ox, and occasionally those of smaller animals were used—*e. g.*, dog, cat, rabbit, guinea-pig, etc.

The conclusions reached as a result of this series of experiments were as follows: In rabbits, guinea-pigs, rats, mice, frogs, and toads, after sufficiently large doses of adrenal extract injected subcutaneously, we get slowed muscular movements, paresis, and finally paralysis of the limbs (hindlimbs always becoming affected first), bleeding from the mouth and nostrils, hæmaturia (not observed in rabbits), breathing rapid and shallow at first, finally becoming deep and infrequent, and occasionally convulsions resembling those of asphyxia preceding death, before which the temperature often falls very low. The paralysis is central. The effects are due to the medulla of the adrenals, the cortex containing no toxic substance. The effects are specific for the adrenal, and not common to other glandular extracts. The toxic material is easily eliminated in some way or other. This accounts for the large dose required to produce a fatal result, and accounts also for the ease with which recovery takes place. Idiosyncrasy plays a large part in the conditions. A partial immunity can be set up by giving doses not sufficient to kill. This immunity passes off after a few weeks.

In dogs the first effect of a subcutaneous injection of an adrenal extract is excitement. There is increased muscular activity, which passes into a stage of agitation with tremors, until paresis and finally paralysis come on. Thirst is also a striking symptom in dogs. There is abundant micturition, but no hæmaturia.

In cats by far the most noticeable result of the injection was an enormously increased rapidity of the respiratory movements in the early stage. Thirst and loss of appetite were recorded, but the paralysis was not so definite as in other animals. In the cat doses sufficient to kill do not raise the blood-pressure within half an hour of injection beneath the skin.<sup>1</sup>

The remote effects noted by Foà and Pellacani, as well as by Oliver and Schäfer, were not noticed in this series of experiments. If the dose were sufficiently large to produce any effects at all, there were some changes in reaction and disposition within a few minutes.

After it had been shown by experimental evidence [Vincent (721, 725)] that the "paired suprarenal bodies" ("medullary" or "chromophil bodies") and the interrenal gland of Elasmobranch fishes correspond respectively to the medulla and the cortex of the adrenal body of the higher vertebrata, and that the "corpuscles of Stannius" of Teleostei consist solely of "cortical" substance, it appeared to be a matter of some interest to test the effects of the two kinds of tissue in Elasmobranchs and of the cortical bodies of Teleosts when extracts of them are injected subcutaneously into small animals [Vincent (724)]. Naturally, only very small quantities of material could be obtained for this purpose, but the effects upon mice were quite definite. The "corpuscles of Stannius" obtained from six specimens of the codfish (*Gadus morrhua*) were found to

<sup>1</sup> Boruttau (129) confirmed this observation, as did also Battelli (79), Lesage (452, 453, 454), and many others. But *intramuscular* injection has been shown by S. J. Meltzer and J. Auer (500) to result in speedier absorption, and therefore a greater rise of blood-pressure than subcutaneous injection. Notwithstanding these observations, Patta (557, 558) states that both intramuscular and subcutaneous injections are inactive if one takes the precaution to avoid the larger bloodvessels.

Lichtwitz (464) states that adrenalin can wander along nerves and travel into a part of the body only connected with the part injected by nerve. Meltzer (495) has been unable to confirm this.

weigh in a moist state 0.4 gramme. These were extracted by boiling with a normal saline solution. The filtered extract was then injected beneath the skin of the back of a mouse. No effects whatever supervened. Next, the "paired suprarenals" of Balfour ("chromophil bodies") from seven specimens of *Scyllium canicula* were found to weigh, when moist, 0.3 gramme. These were similarly extracted, and the filtrate administered to the same mouse (which had remained in perfect health) a few days later. The animal was immediately and powerfully affected. The breathing became very rapid, the limbs became weak, the temperature lowered, and death with convulsions ensued in less than five minutes. Extracts of the elasmobranch inter-renal gland produced no effects when injected in the same manner. A further experiment with material obtained from *Raja clavata* gave harmonious results.

These experiments gave further positive evidence of the homology of the "paired bodies" of Elasmobranchs with the medulla of the mammalian adrenal, and, in conjunction with the morphological and histological evidence as to the homology of the "inter-renal" and the "corpuscles of Stannius" with the cortex of the mammalian adrenal [Vincent (720, 728), Balfour (64), Diamare (210, 211)], show that the toxic effects of subcutaneous administration of adrenal extracts are obtained only with chromophil substance, whether forming the medulla of the adrenal or the paired chromophil bodies of Elasmobranch fishes.

Wybauw (770) considers that extracts of the adrenals of guinea-pigs are less toxic than extracts from the glands of other animals.

An important observation was made by Blum in 1901 (116). After subcutaneous or intravenous injection of adrenal extracts, glycosuria occurs, even when the animals injected are being fed upon a diet free from carbohydrates, or after several days' inanition, when it is to be supposed that all the glycogen must have disappeared from the liver. The author considers that the function of the adrenal is to free the organism from the poisonous products of metabolism.

More recently the purified active principle of the chromophil tissues (under various names, perhaps most commonly

“adrenalin”) has been employed for subcutaneous and other modes of injection instead of the crude extracts. The results have not been very different from those obtained when extracts of adrenal medulla were used. Amberg<sup>1</sup> (46) could find no difference in action between Abel’s “epinephrin” and Takamine’s and Aldrich’s “adrenalin.” Working with dogs, Amberg obtained practically the same symptoms with intravenous, intraperitoneal, or subcutaneous administration.

The immunity first observed by the present writer, working with adrenal extracts, has been recently recorded by Ssaweljew (663), who employed pure adrenin.<sup>2</sup>

Since Blum’s original communication (116) numerous papers upon adrenal glycosuria have appeared, and the majority of workers have used, not extracts of the adrenal or of chromaphil substance, but the pure active substance (adrenin). Among these writers may be mentioned Zuelzer (775), Metzger (504), Herter and Richards (360), Paton (556), and Lazarus (447).<sup>3</sup> The last-named observer states that after prolonged administration of adrenin there is marked hypertrophy of the islets of Langerhans, of the pancreas, as well as of the adrenal bodies.<sup>4</sup> Herter and Richards, and also Paton, confirmed Blum’s observation that, as with phloridzin and pancreatic diabetes, glycosuria occurs even when stored carbohydrates have been previously eliminated. As pointed out by Schäfer, there seem to be connecting links between the glycosuria set up by pancreatic removal and that due to the action of adrenalin. Herter and Wakeman (361) found that quite small amounts (1 c.c. of a 1 in 1,000 solution) of adrenalin applied to the pancreas provokes marked glycosuria.

According to Mayer (491, 492) and Frouin (277), as already noted (*vide supra*, p. 142), neither the puncture diabetes nor

<sup>1</sup> See also Battelli e Taramasio (83) and Batelli (79).

<sup>2</sup> See also Pollak (590) and Waterman (738, 739). The last-named author succeeded by injecting rabbits with larger and larger doses of *r*-suprarenin in bringing the animal into a condition in which they cannot be rendered glycosuric by means of *l*-suprarenin. This paper (396) contains a discussion of the subject and references to other papers. Fröhlich (275, 276) had previously reported that intravenous injection of *d*-suprarenin renders animals insusceptible to the pressor effects of *l*-suprarenin or of adrenalin.

<sup>3</sup> See also Velich (717).

<sup>4</sup> Benedicenti (87) affirms that subcutaneous injection of adrenalin diminishes the flow of pancreatic juice.

pancreatic diabetes occur after extirpation of the adrenals. Zuelzer (775, 776) has gone so far as to definitely assign an adrenal origin to the pancreatic diabetes of Mehring and Minkowski. He found that extirpation of the pancreas carried out at the same time as ligature of the adrenal veins provokes little or no glycosuria. Injection of certain doses of adrenalin remains without effect if one injects at the same time a dose of pancreatic extract. In dogs, if the pancreas and the adrenals are simultaneously extirpated, there is no glycosuria. Zuelzer also made some experiments with an artificial circulation through the liver. He concludes that the adrenal secretion is normally neutralized by the pancreas, and that pancreatic diabetes is really a "negative pancreatic diabetes," while it may be regarded as a "positive adrenal diabetes," the real stimulus to the genesis of glycosuria being the adrenal secretion.

Similar views are held by Frugoni (278, 279, 280, 281, 282, 283), who found that pancreatic juice destroys adrenalin *in vitro*. Other authors connect the adrenin glycosuria with the functions of the thyroid and the action of the sympathetic nervous system [Waterman and Smit (743), Eppinger, Falta, and Rudinger (241)].

Loewi (472) reports that in diabetes arising after extirpation of the pancreas adrenalin produces dilatation of the pupil if applied to the conjunctiva, whereas it has no influence on the normal eye. This observation was confirmed by Biedl and Offer (107), and it is stated that this reaction may be used as a diagnostic sign of pancreatic diabetes.

In 1898 Biedl (101, 102) discovered a new form of experimental diabetes. This was induced by tying the thoracic duct or by leading it to the exterior and allowing the lymph to flow away. The author considers that the lymph which constantly flows into the circulation from the lymphatic duct contains a substance which influences directly or indirectly the supply of sugar in the organism. Biedl and Offer (107) find that in this form of diabetes also the pupil reacts to adrenalin dropped on the conjunctiva. They further find that admixture with lymph or simultaneous injection of lymph from another animal prevents both the adrenin diabetes and the mydriatic reaction. In this relation Schäfer (625) recalls the observation of Lépine (449)



that in pancreatic diabetes the injection of lymph from a normal animal produces marked temporary diminution of sugar in the urine. Schäfer suggests that the lymph normally contains a chemical (glycolytic ?) substance, derived from the islets of the pancreas,<sup>1</sup> which substance is essential to the due maintenance of normal carbohydrate metabolism. This whole question has recently been complicated by Pfüger's announcement of a "duodenal diabetes" (*vide supra*, p. 39). It seems possible that the final solution of the problem may be arrived at by an accurate knowledge of the interaction between the adrenals and the pancreas through the mediation of the sympathetic nervous system.

S. J. Meltzer and Clara Meltzer Auer (498, 499, 501) found that subcutaneous injections of adrenalin, which normally are without effect on the pupil, produce marked dilation after removal of the superior cervical ganglion.

Underhill and Closson (704) could not find any change in the nitrogen of the urine in adrenin glycosuria, such as was recorded by Paton.

Gautrelet and Thuan (300) state that heat polypnoea hinders the onset of adrenin glycosuria, while warmth alone does not. This result appears to depend on the destruction of the adrenin by the increased chemical processes of the body, due to the polypnoea.

Agadschanianz (31) finds that intraperitoneal injection of adrenalin in rabbits causes the glycogen to disappear from the liver and muscles, or at any rate reduces its amount. So also record Doyon, Morel, and Kareff (221), and others [Gatin-Gruzewska (292), Doyon and Gautier (220)].

Drummond (223) reports that after administration of adrenalin there occur congestion of organs and histological changes, indicating that the substance acts as a protoplasmic poison.

Oliver and Schäfer (539) suggested that the material obtained from the adrenal medulla, which produces death, is of a different nature from that which has such a powerful effect upon the blood-pressure. The paralysis is due to the action of the poison upon the central nervous system. The present writer (727) came to the conclusion that the adrenal body contains an active principle which acts both centrally

<sup>1</sup> See, however, a discussion of this point in an earlier chapter (*vide supra*, p. 40 *et seq.*).

and peripherally. The central action is produced most probably upon the motor centres of the brain, while the peripheral action is shown by the effect upon blood-pressure when the extract is injected intravenously. The question naturally arises whether both these effects are due to one substance or whether there are two active materials present in adrenal extracts. It seems to be generally admitted at the present time that the toxic effects, like those on the blood-pressure, are due to the action of adrenin. If this be the case, it would seem that this substance has a central as well as a peripheral action.

Elliott (237) discusses the effects of subcutaneous injections of adrenin, and classifies the possible causes of the symptoms under three heads: (1) The strain thrown upon the circulatory system by the great rise of blood-pressure; (2) a poisoning of tissues by quantities of adrenin exceeding that sufficient for physiological stimulation; (3) the poisonous action of possible decomposition products of adrenin within the body. The author considers that the chief cause is No. 2—*i.e.*, that the excess of adrenalin itself is toxic. He points out that a poisonous action of adrenin on bioplasm is suggested by its chemical constitution, which displays the  $-NH.CH_3$  grouping that resists chemical alteration in the body with great stubbornness.

Ssaweljew (663), as we have seen, confirmed the observation of the present writer that some immunity can be established by administering doses of adrenin not sufficient to cause death. But Ssaweljew reports further that he could obtain an immune serum which was capable of conferring passive immunity upon a second animal. Stradiotti (674), employing the "paraganglina Vassale," produced in dogs a serum which could precipitate the "paraganglina" and neutralize its power of vasoconstriction. Elliott and Durham (238) point out that these results are not in accordance with expectation, for as yet no instance has been discovered of the production of an antibody to a substance of such chemical character as that of adrenalin. In their experiments no trace of an anti-adrenalin could be found.<sup>1</sup>

<sup>1</sup> Baduel (62) found no change in the blood-serum of rabbits injected with adrenalin, and Abbot (1, 2) failed to discover any body other than a hæmolysin in rabbits injected intraperitoneally with an extract of guinea-pigs' adrenal bodies. See also Gildersleeve (316) and Levi della Vida (455).

2. *The Special Physiological Effects of Extracts of Adrenal Medulla and of Adrenin.*

1. *The Effects upon the Heart and Arteries.*—A new stage in the history of our subject was reached in the year 1894 by the discovery by Oliver and Schäfer (537, 538, 539) that extract of the medulla of the adrenal bodies produces a very remarkable rise of the blood-pressure on injection into the circulation of a living animal.<sup>1</sup>

Oliver and Schäfer employed glands mainly from the calf, but also from the sheep, the guinea-pig, the cat, the dog, and man. The physiological effects noticed were identical in all, the only difference being in the case of diseased adrenals in man (Addison's disease), in which case, if the disease were extensive, no effect whatever was obtained. Extracts of the glands were prepared with water, with alcohol of various strengths, with glycerin, with ether, nigröin, and various other solvents. They were made either by digesting an ascertained weight of the fresh gland or of the dried gland in these menstrua, or in addition by boiling the infusion for a few minutes. The animals experimented upon were chiefly dogs, but some experiments were also made upon cats, rabbits, and guinea-pigs, and one upon a monkey. The extracts were usually administered by intravenous injection, and the effects upon the arterial system determined by the mercurial kymograph, various kinds of plethysmographs, and perfusion through the arterial system of the frog, after the nervous system had been destroyed.

The chief and fundamental effect noticed was *contraction of the arterioles*. This contraction is so great as to produce (even when concomitant vagus action has caused a great diminution in the rate and force of the heart's beats) a *large rise of blood-pressure*, and, in the case of the frog with its nervous system destroyed, almost complete cessation of the flow of circulating fluid through the arterioles.

The usual effect of the injection is to produce constriction of isolated organs. The limb shrinks (see Fig. 40), the kidney and spleen contract considerably, while the heart

<sup>1</sup> An interesting account of the history of the discovery is given by Schäfer (626).

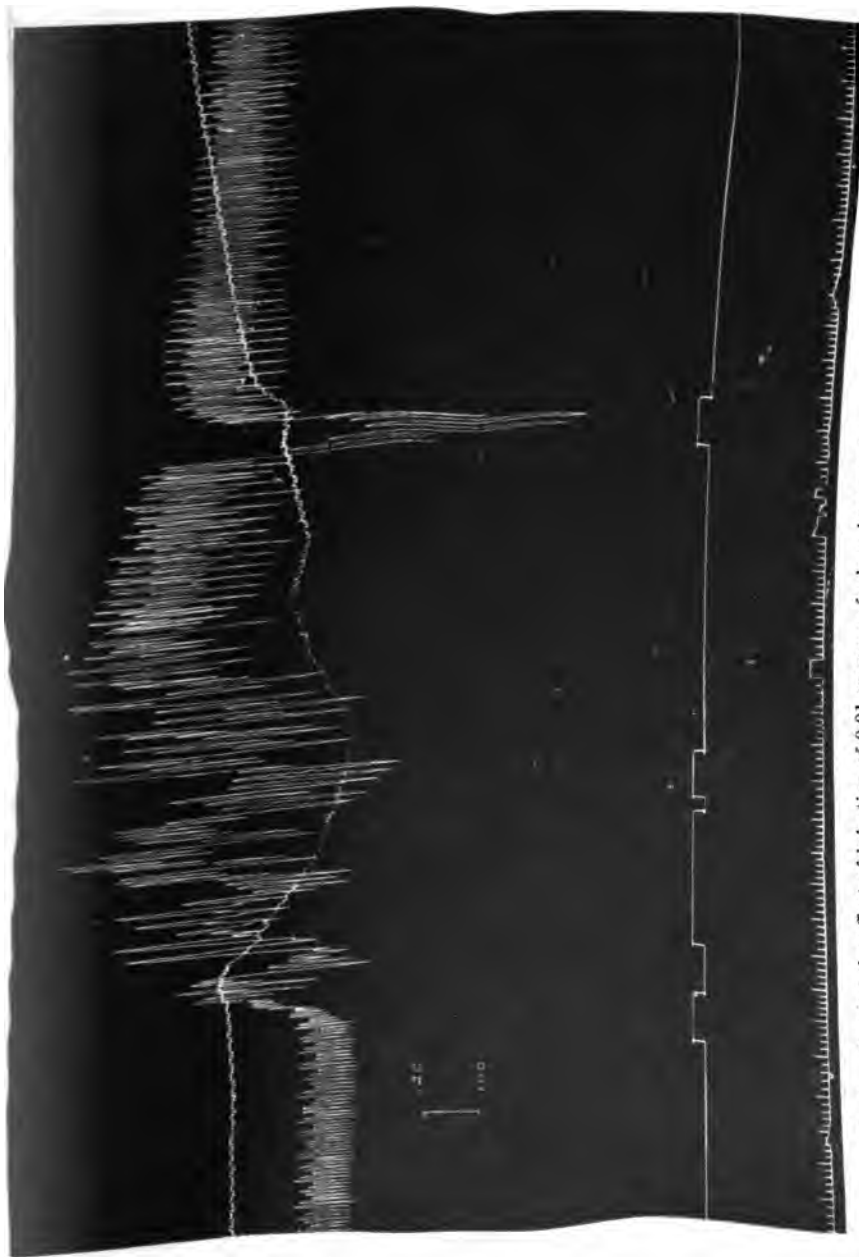


FIG. 40.—Tracing showing the effect of injection of 0.01 gramme of adrenal extract into a vein of a dog weighing 15 kilogrammes. Ether and morphine. The lower curve is that of the carotid blood-pressure, the upper one that of the volume of the left hind-limb. At the second and third signals the vagus was stimulated.

and larger bloodvessels are enormously distended. But sometimes a limb expands, and in some experiments one limb contracts while another expands. In the later stages of experimentation the passive dilatation is more usual. The rise of blood-pressure is very largely due to constriction of the splanchnic arterioles. But sometimes the intestine expands (see Fig. 43). In some cases Oliver and Schäfer noticed in organs enclosed by a plethysmograph an apparent struggle between the diminution in size resulting from contraction of the arterioles and the expansion due to swelling of the larger bloodvessels, and some of their curves show a passive dilation at the beginning of the effect of an injection, followed by a prolonged diminution in size due to a more marked contraction of smaller arteries having supervened. The medium-sized arteries also participate in the dilation.

The contraction of the arterioles occurs in a frog with its nervous system destroyed, as stated above. It also occurs after section of the spinal cord and after section of the nerves going to the limb. Therefore the contraction must be due to the direct action of the active principle of the adrenal medulla upon the muscular tissue of the bloodvessels. This question as to the precise tissues upon which adrenin acts will be referred to again later on.

The rise of blood-pressure occurs after a certain interval of latency (twenty seconds in the dog) occupied by the passage of the extract from the vein into the arteries. The rise takes place, whether the vagi be cut or not, and whether atropin has been injected or not. But it is much greater after section of the vagi or after injection of atropin, because of the concomitant effect upon the cardiac inhibitory centre in the medulla (see Fig. 42). The rise is rapid, but only lasts a few minutes. During the rise the Traube-Hering curves are abolished, and in the cat and the rabbit the effect of stimulation of the depressor nerve is in abeyance.

But the rise of blood-pressure is due not only to constriction of arterioles, but also to *increased rate and energy of heart-beat*.

Another striking phenomenon noticed by Oliver and Schäfer was *cardiac inhibition through the vagi*. Sometimes in the earlier stages of the action of the extract the heart,

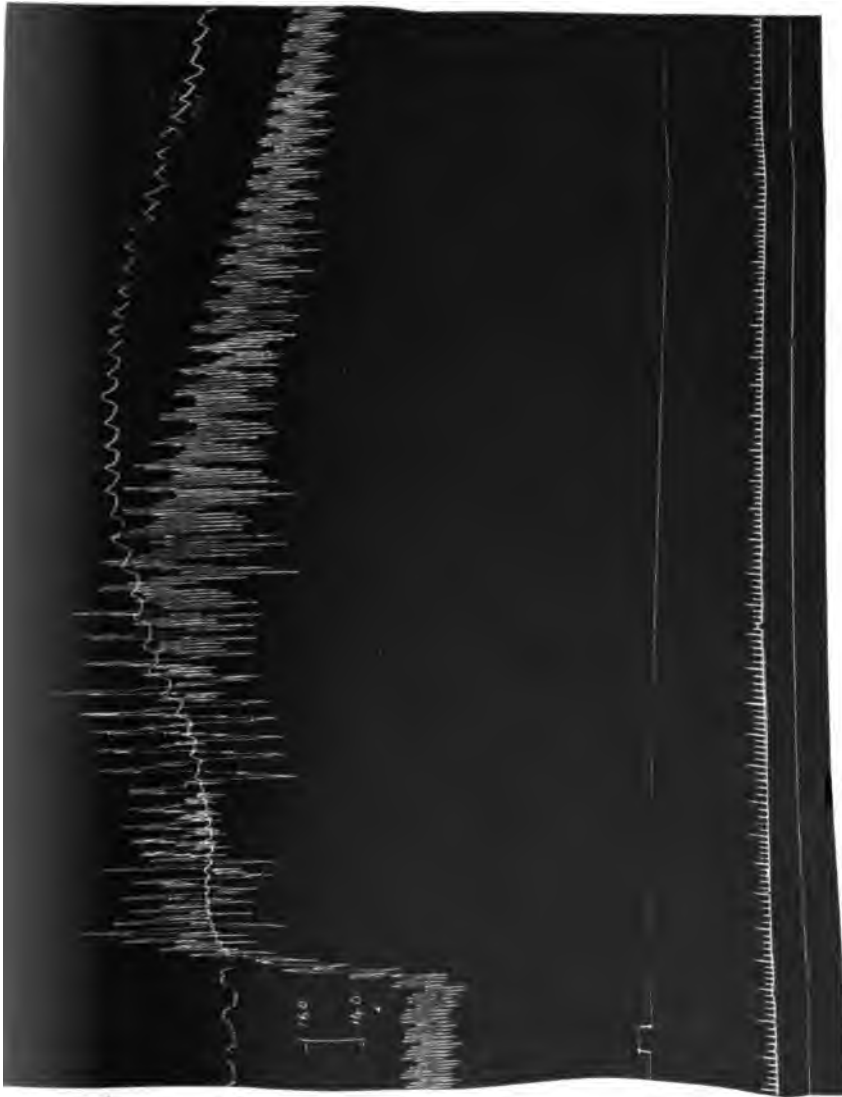


FIG. 41.—Tracing showing the effect of the injection of 0.005 gramme nicotine into a vein of a dog, 13.5 kilogrammes. Lower curve indicates carotid blood-pressure, upper one is the volume of intestinal wall. Cf. this with Fig. 40. Ether and morphine.

instead of being augmented and accelerated, is strongly inhibited. When the vagi are cut or atropin administered, this effect is abolished, and the constriction of the arterioles, combined with the augmentation of the heart, produces an enormous rise of the blood-pressure. The cardiac inhibition is of central origin, but the augmentation is due to the direct action on the heart. Sometimes the inhibitory effect is shown only after a few minutes. The effects obtained

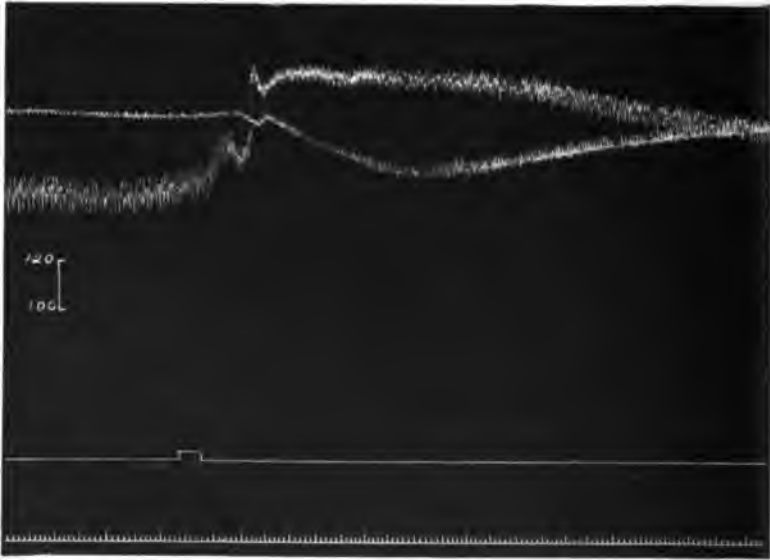


FIG. 42.—Tracing showing the effect of adrenalin after previous administration of a dose of atropin. Dog, 15 kilogrammes. Ether and morphia. Lower curve is that of the carotid blood-pressure, upper one the volume of the left hind-limb.

with the isolated frog ventricle were less striking than those in mammals.<sup>1</sup>

Finally, it was proved by these authors that extracts of the cortex of the gland are quite inactive, *the active principle being confined strictly to the medulla*. Their general conclusion was that the medulla of the adrenal secretes a material whose action is to increase the tone of all muscular tissue, and especially that of the heart and arteries.

<sup>1</sup> This same result has recently been obtained by Gatin-Gruzowska and Maciag (293, 294), who employed pure adrenin. These authors, however, misstate the results obtained by Oliver and Schäfer.



FIG. 43.—Tracing showing the effect of injection of adrenal extract after previous administration of nicotine. Dog, 13.5 kilogrammes. Ether and morphine. Upper curve shows volume of intestinal wall.



Nearly a year later than the first preliminary communication of Oliver and Schäfer (537) appeared the communications of Szymonowicz and Cybulski (685), and still later, fuller accounts by these authors (683, 684, 686, 687). The Polish physiologists had no knowledge of the previous work of Oliver and Schäfer; they observed many of the same phenomena, and brought independent corroboration of many of the observations. But in some details and upon one important point they obtained different results; they considered that the extract produces its vasoconstriction effects not peripherally, but centrally upon the centres in the medulla. This was, as has been proved by all subsequent investigations, an erroneous conclusion. As we have already seen, Oliver and Schäfer showed conclusively that the effects could be induced in an animal from which the central nervous system had been completely removed.

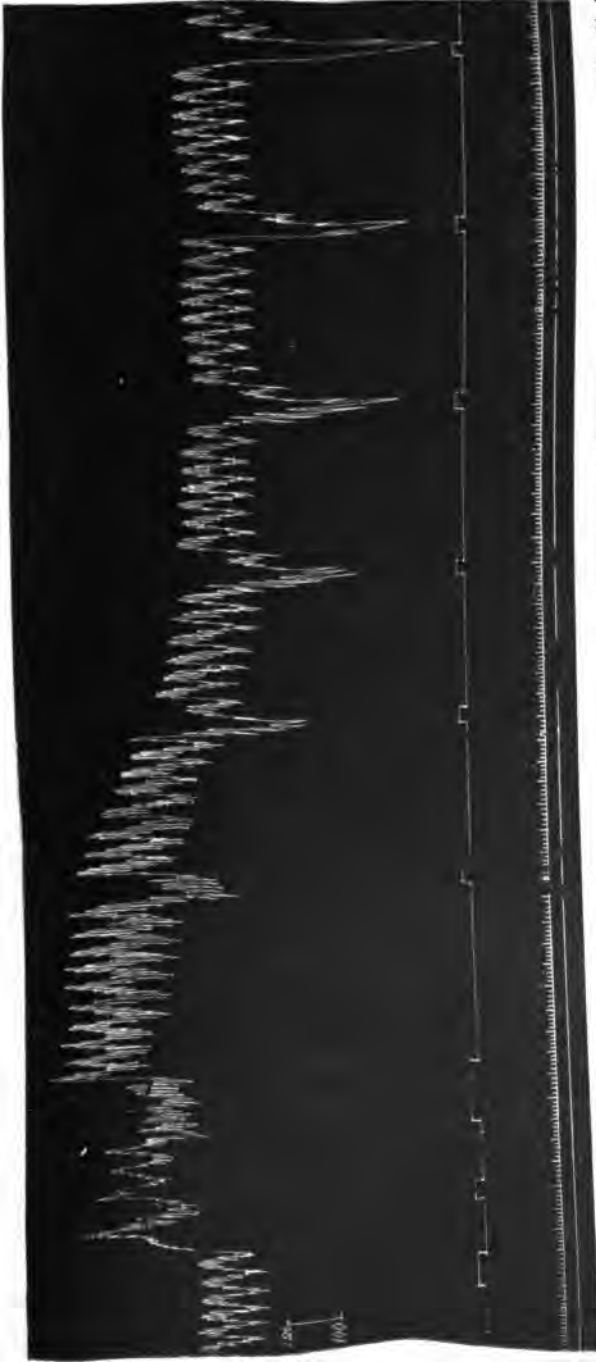
So far as the hæmodynamic effects of adrenal extracts are concerned, the papers of Oliver and Schäfer gave an accurate account of all the fundamental facts, and there is little or nothing to add to their account up to the present time.

One of the first to confirm the statement of Oliver and Schäfer that the vasoconstrictor effect is peripheral and not central was Biedl (99).

Among other papers of this period confirming the general results of the English observers may be mentioned those of Velich (709, 710, 711), Gottlieb (321), Fränkel (266), and Ocaña (533). Fuller accounts are given by Langlois (442) and Boruttau (129).

It had been shown by Gourfein (328) and by Cybulski (685) that adrenal extract in sufficient dose paralyzes the vagus (see Figs. 40 and 44). This was confirmed by Langley (435). The paralysis is brief. In the cat 5 to 10 c.c. of 1 per cent. extract of dried adrenal cause, as a rule, paralysis for from thirty seconds to one or two minutes. When a dose is given a little short of that required to make stimulation of the vagus ineffective, the respiratory curves disappear, and there is a gradual fall of pressure. This result is probably due to weakening of the heart-beat without much variation in rate.

According to Oliver and Schäfer (539), injection of extract



**FIG. 44.**—Tracing showing the paralyzing effect of adrenal injection upon the vagus nerve. The nerve was stimulated at the points signalled during the height of the blood-pressure, and at various points during the fall. It is seen that when the blood-pressure is at its highest point, stimulation of the vagus produces practically no effect. This effect becomes gradually more marked as the pressure falls, till on the last occasion of stimulation the effect obtained is the normal one.

in the dog after section of both vagi causes only quickening of the heart-beat. In the cat Langley found that after section of the vagi adrenal extract sometimes causes quickening only, but that sometimes the rate is irregular, and in one case the heart stopped for three minutes. The slowing, when it occurs, is, Langley thinks, due to the increased work thrown upon the heart; whether the action is entirely direct on the heart muscle or is partly due to a post-ganglionic axon reflex, there is hardly sufficient evidence to show, but the slow beats caused by the extract are fewer or absent after injection of nicotine, although the rise of blood-pressure is commonly higher.

As pointed out by Oliver and Schäfer, the extract does not act equally on all the arteries; its effect is perhaps greatest upon those of the splanchnic area, and its action in general runs parallel with the action of the sympathetic nerves on the bloodvessels. Thus, injection of adrenal extract causes great pallor of the uterus and but little of the bladder. It has a strong action on all skin arteries; and on all medium-sized arteries in the body. In the abdominal viscera its effect is great on the main branches of the cœliac and superior mesenteric arteries.

The primary effect of adrenal extract on the vessels of the submaxillary gland is constriction. The gland becomes pale and remains so for thirty seconds. Then it becomes flushed, and the flushing lasts longer than the secretion caused by the injection. The pallor is not so great as that produced by stimulating the cervical sympathetic, nor is the flushing so great as that produced by stimulating the chorda tympani. Both of these nerves have much their usual action on the blood-flow, if stimulated while the secretion is going on.

In the dog pallor of the bucco-facial region is produced by adrenal extract. This is the effect produced by weak stimulation of the cervical sympathetic [Langley (435)].

Brodie and Dixon (138) were unable to obtain evidence of constriction of the pulmonary vessels on injection of adrenalin, and thought this was because the pulmonary arterioles possess no vasomotor nerve-supply. (Adrenalin, they considered, acts on the nerve endings.) Plumier (581), using larger doses, succeeded in getting a positive result—

that is to say, he recorded some constriction of the pulmonary vessels on injection of adrenalin; but, according to Schäfer (625), the action is far less than upon the sympathetic vessels.<sup>1</sup>

It was stated by Spina (658) that the injection of adrenal extract causes reddening of the brain, so that the peripheral vessels were not constricted;<sup>2</sup> but Wiggers (760, 761), using the isolated dog's brain and perfusion with Locke's fluid containing adrenalin, has been able to observe a diminution of the outflow of fluid, from which he concludes that the brain possesses vasomotor nerves, and that adrenalin acts on the ends of these. As for the coronary vessels, it is usually stated that adrenalin does not constrict these. Schäfer (624) correlated this with the absence of vasoconstrictors from the cardiac accelerators, and concluded that, with both forms of excitations, was produced quickening of the flow through the coronaries. Elliott (237) suggests that in the beating heart such an action cannot be dissociated from a possible secondary dilatation by metabolites from the increased work of the heart muscle. He states that when perfusing a strip of the cat's ventricle by a single coronary artery he has seen almost instant increase of flow after addition of adrenalin to the Locke's solution used. This occurred with a strip that did not beat, and therefore independently of muscular metabolites. Langendorff (433) has recently immersed strips of the vascular wall attached to a lever in adrenalin solution; he states that whereas strips from the arteries so tested contract when adrenalin is brought in contact with them, a strip from a coronary artery will become relaxed, and he infers from this that adrenin produces inhibition and therefore vasodilation. Langendorff points out that from a teleological standpoint this is advantageous; since the adrenin increases the force of the heart-beat, it must be favourable for this action that the calibre of the vessels in the heart-wall becomes increased. Schäfer (625) has, however, not succeeded in

<sup>1</sup> Petitjean (566), without denying the accuracy of the results obtained by Plumier, insists that the constriction, if it occurs, is very temporary, and soon gives place to a passive and intense dilation. Wiggers (763) has recently come to the conclusion that adrenalin does actually constrict the pulmonary vessels when the adrenin solution has the same viscosity as the perfusion-fluid.

<sup>2</sup> See also Dixon and Halliburton (213).

obtaining the result described by Langendorff, and suggests that possibly there might have been some other substance than adrenin in the solution used.

Moore and Purinton (513) have recorded a *fall* of blood-pressure instead of a rise when very small doses of adrenal extract are administered. Other authors<sup>1</sup> have from time to time made reference to a depressor constituent of the adrenal. This is not to be wondered at when we remember that, as first noted by the present writer, extracts of tissues generally lower the blood-pressure; but the presence of a depressor constituent will not explain the result obtained by Moore and Purinton, for there is no apparent reason why the depressor effect should not be swamped by the pressor with small, just as with larger, doses. Pari (552, 553) finds that with freshly prepared extracts there is never a lowering of the blood-pressure, but that with very dilute solutions, which have been kept for some time, this may sometimes be observed. He suggests, therefore, and very reasonably, that the depression described by Moore and Purinton was due to chemical changes in the adrenalin in the dilute solution. Pari supports the view of Hunt, that the depressor substance is choline.<sup>2</sup> It is not clear to the present writer how any depressor effect of chromaphil tissue extract can be manifested unless it be subjected to some treatment which causes a chemical change either in the adrenin, so as to reduce its pressor effect, or in the depressor substance or substances, so as to increase the depressor effect.

It has been mentioned above that the "paired supra-renal bodies" of Elasmobranch fishes yield an extract which produces the same physiological effects as adrenal medulla [Swale Vincent (721), 1897]. In 1898 Langlois (441) showed that the adrenals of the frog (which contain masses of chromaphil cells) contain an analogous substance and are functionally homologous with the glands of higher vertebrates. Biedl and Wiesel (108) proved that the "Neben-

<sup>1</sup> Gürber (339), Hunt (371).

<sup>2</sup> On the question of choline in animal tissues see p. 26 *et seq.* The depressor effect of adrenal extract has never been noticed by the present writer, although very small doses have frequently been employed. It seems more than doubtful whether the depressor substance of the adrenal body is choline. It is much more probable that it is of the same nature as that described above (p. 26), and which has since been called "vasodilatin" by Popielski.

organe" of Zuckerkandl contain the active substance. The present writer (731) has further shown that the "abdominal chromaphil body" of the dog also contains the pressor substance. Mulon (525) has raised the blood-pressure of an animal by injection into the circulation of an extract made from the carotid body of the horse (which body was shown by Stilling to contain chromaphil cells). It seems clear, therefore, that all chromaphil tissues, whether contained in the adrenal or not, yield adrenin, or a substance having similar chemical and pharmacodynamical properties.<sup>1</sup> How far this conclusion may be adduced, in conjunction with other observations, as evidence of an internal secretion on the part of all these tissues, is a matter for subsequent consideration (see p. 213).

A pathological effect which has been noted by Josué (383) as a result of repeated injections of adrenin into the auricular vein of the rabbit is a degenerated condition of the wall of the larger arteries, especially of the aorta (arteriosclerosis). Atheroma, calcification, and even aneurisms are also described, and the changes have been recorded in the pulmonary and other arteries. According to Schäfer (625) these effects are not peculiar to adrenin, but are produced by other blood-pressure raising substances, such as digitalin and nicotine. According to Elliott (237) "mechanical strain is doubtless the cause of the atheromatous lesions which develop after repeated intravenous injections. These occur in the coronary arteries which are not contracted by adrenin, and must, therefore, be widely distended in the general rise of blood-pressure" (see p. 173). But Batty Shaw (646) is of a different opinion. He states that if adrenin is injected with an amount of amyl nitrite which is just capable of neutralizing its pressor effects, arterial disease identical with that produced by adrenin alone is manifested—in other words, adrenin produces its effects not because of its pressor tendency, but from some other much more subtle influence. "We have no experimental grounds for believing that persistence of any stimulus should at length lead to degeneration

<sup>1</sup> Of course, this conclusion is based upon the provisional assumption that "chromaphil" tissues are specific in their nature, and are everywhere of the same essential character. It is not out of the question, however, that there may be some cells which stain brown with bichromate, which are, nevertheless, of a different character.

instead of hypertrophy of the middle coat" [Batty Shaw (646)].

Braun (133) described the degenerative changes in the arteries in considerable detail, but Kaiserling (391) does not attach much importance to the effects so far as the rabbit's aorta is concerned, because, he says, such changes sometimes occur in rabbits not treated with adrenin [Israel (372), 1881]. Etienne and Parisot (248) have come to the conclusion that elevation of the blood-pressure is not in itself sufficient to induce atheroma. This effect is of a toxic nature.<sup>1</sup>

Klotz (401) has recently made the important observation that, by periodic suspension of rabbits for a few minutes daily by the hind-legs most advanced aortic lesions can be induced, while Biedl and Braun (106) record typical degenerative changes in the aorta and its branches, as a result of repeated compressions of short duration.<sup>2</sup> The experiments which have been performed up to the present time do not enable us to decide what is the precise actual cause of the arterial changes after repeated injections of adrenin.<sup>3</sup> There seems no reason why both the principal causes alleged—viz., a toxic action and a mechanical strain—should not both have a share in the production of the result.<sup>4</sup>

De Bonis (127) records changes in the heart muscle after adrenin injections.

<sup>1</sup> Other papers on this subject previous to the date of the communication of Etienne and Parisot are: Adler und Hensel (30), Biland (111), Loeb und Fleischer (468), Baylac et Albarède (85), Kalamkarov (394), Kleinenberger (400), Etienne et Parisot (245, 246), Gilbert et Lion (135), Etienne et Parisot (247), Schrank (637), Richon et Perrin (604).

<sup>2</sup> Bonnamour and Thévenot (128) seem to think that the properties which induce vasoconstriction, atheroma, and poisonous effect are all distinct.

<sup>3</sup> Venulet and Dimitrowsky (718) find that potassium iodide acts in an inhibitory direction upon the secretion of adrenin. This is the reason, in the opinion of the authors, that this substance lowers the blood-pressure, and is of therapeutic benefit in arterio-sclerosis. Calcium chloride, although in many respects a true antagonistic of adrenin, does not appear to prevent the occurrence of arterio-sclerosis (Schrank, 636).

<sup>4</sup> Other papers dealing with the action of adrenal extracts and of adrenin on the heart and bloodvessels are: Cyon (202), Bardier (67), Velich (713, 714, 715, 716), Guinard et Martin (342, 343), Gerhardt (301), Camus et Langlois (155), Mathieu (488), Carnot et Jossierand (163), Neujean (528).

E. Koll (417) reports that continuous injection of adrenin will produce a continued rise of blood-pressure. Kahn (387) has recently studied, by means of the electrocardiograph, the detailed effect of adrenin upon the heart.

2. *The Effects on other Structures, and the Mode and Seat of Action of Adrenin.*—Oliver and Schäfer (539) investigated the effects of adrenal extracts on the *respiration* of the rabbit and the dog. Similar results were obtained in both, but the effect is most marked in the rabbit. It occurs soon after the administration of the drug, and may result in arrest of respiratory movements for a short time. More commonly, however, there is produced a shallowing of the respirations, which persists for a certain period and then gradually passes off. In the dog no stoppage of respiration was ever obtained, but the respirations, although proceeding with an ordinary rhythm, were for a few times slightly shallower. Other observers have also noted this effect of adrenal extracts upon the respiration. Langley (435) states that it is nearly always most marked with the first injection; with repeated injections the effect as a rule soon becomes trivial, and always becomes so if the injections are repeated a sufficient number of times. The subject has been recently investigated by Langlois and Garrelon (445). These authors seem to have obtained greater effects in the case of the dog than did Oliver and Schäfer; they report that if adrenalin be injected into a dog, expiratory apnoea sets in simultaneously with the beginning of the rise of blood-pressure. The duration of this apnoea is not constant. In most cases the respiratory movements begin again while the blood-pressure is still very high, and the respiration has most frequently returned to its regular type before the blood-pressure has returned to normal. If the injections are repeated in rapid succession, the influence disappears (confirmatory of Langley). Langlois and Garrelon report that after section of the vagi, the adrenalin injection has a much less marked action on the respiration. There is then a slowing of the movements, but no apnoea. Air rich in oxygen favours the occurrence of this apnoea, while an atmosphere with a large proportion of carbon dioxide hinders it.

Oliver and Schäfer (539) discovered that adrenal extracts *prolong the curve of contraction of the skeletal muscles*, both in the frog and in the dog, though the period of latency is not increased. They were convinced that the curve is not a fatigue curve, but that it is comparable rather to the



effect of a slight dose of veratrine. This effect has since been noted by many observers. Boruttau (130) says that the phenomenon occurs in excised curarized muscle, and reminds one of the first stage of fatigue. Panella (550, 551) describes an anticuraric action of adrenin ("hemostasine") and states that it ("myosthenin," on this occasion) increases the activity of fatigued striated muscles.

Lewandowsky (458, 460) found that intravenous injection of adrenal extracts produces *dilatation of the pupil*, withdrawal of the nictitating membrane, protrusion of the eyeball, and slight opening of the eyelids. The last two symptoms are usually less marked than the action on the pupil and the nictitating membrane. The effects produced on the smooth muscle of the eye and the orbit are, in fact, the same as are called forth by stimulation of the cervical sympathetic. There is a short latent period, and the effects usually last some minutes, the period of duration being prolonged by cooling the animal. The action is peripheral, although local application to the eye is without effect. The experiments were performed upon cats. The same observer also recorded *excitation of the arrectores pili* and *inhibition of the bladder*.

Boruttau (129) confirmed the observation as to the occurrence of dilatation of the pupil on intravenous injection of adrenal extract, and observed that in the cat subcutaneous injection produces no effect upon either the blood-pressure or the pupil. This writer further recorded that the injection causes *inhibition of intestinal movements*.

Lewandowsky pointed out that the extract is still effective after the superior cervical ganglion has been excised, and the nerve fibres proceeding from it allowed to degenerate. He concluded from this that the extract must stimulate the muscle substance directly, and not by means of the nerve endings.

Langley (434, 435) confirmed this observation of Lewandowsky, and agrees that the various eye effects are produced by a direct action of adrenal extract on the unstriated muscle. This author also found that the extract *excites the salivary and lachrymal glands, the liver, the muscular tissue of the uterus and vagina, of the vas deferens, the vesiculæ seminales, the dartos, and the muscular coat of the stomach.*

*In the stomach inhibition of the muscular movements is produced.* According to Langley, the effects produced by adrenal extract in the cat and rabbit may be arranged roughly in the following order as regards the amount of extract required per body weight to produce an obvious effect :—

Rise of blood-pressure.

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Inhibition of the sphincter of the stomach and of the intestine (rabbit).

Inhibition of the bladder.

Dilation of the pupil (cat).

Withdrawal of the nictitating membrane (cat) } Slightly less readily than the  
Separation of the eyelids (cat) } foregoing.

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Contraction of the uterus, vas deferens, seminal vesicles, etc. (rabbit).

Salivary and lachrymal secretion.

Inhibition of the stomach.

Inhibition of the gall-bladder and increased bile secretion.

Dilation of pupil (rabbit).

Inhibition of internal anal sphincter (rabbit).

Contraction of internal anal sphincter (cat) } Effects relatively slight.  
Contraction of internal generative organs (cat) }

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Contraction of the muscles of the hairs.

---

Contraction of tunica dartos of scrotum } No certain effect.  
Secretion of sweat. }

Langley divides the autonomic nervous system into sympathetic, cranial, sacral, and enteric, and points out that the effect of adrenal extract in no case corresponds to that which is produced by stimulation of a cranial autonomic or of a sacral autonomic nerve. On the other hand, *the effects produced are almost all such as are produced by stimulation by some one or other sympathetic nerve.* Notwithstanding this, he is inclined provisionally in his paper written in 1901 to favour the view that adrenalin acts directly on muscle fibres and gland cells, but leaves unanswered the question as to why the action in the several cases should correspond so closely with that caused by stimulation of the sympathetic nerves.

Kuliabko and Alexandrowitsch (430) state that adrenin increases the tonus of the intestinal muscle and calls forth "pendulum contractions."<sup>1</sup>

<sup>1</sup> See also Doyon (219).

Apocodeine abolishes the effects produced by sympathetic excitation, and was found by Dixon (212) to abolish those produced by adrenalin. He therefore concluded that adrenalin acts upon sympathetic nerve endings. It has been shown that in Mammalia, if the vagi have first been paralyzed with atropin, adrenal extract produces an augmented systole and acceleration of the heart [Oliver and Schäfer (539), Gottlieb (322), Hedbom (357), Cleghorn (182)]. Both of these effects of adrenalin may be abolished by the injection of large doses of apocodeine. Thus, Dixon found that in a cat  $\frac{1}{2}$  c.c. of a 1 in 30,000 solution of adrenalin increased the heart-rate from 92 to 211 per minute. After the injection of 100 milligrammes of apocodeine the same injection of adrenalin now only increased the rate from 93 to 101 per minute. A further injection of 200 milligrammes of apocodeine was then administered, and caused the rate of the heart to diminish to 87 per minute. Adrenalin now, even in large doses, produced no acceleration, and there was no augmentation of the systole. Dixon therefore concludes that the whole effect of adrenal extract on the heart is a stimulation of the sympathetic nerve endings. Similarly, the vasomotor nerve endings are paralyzed by apocodeine, and after the administration of this drug no vasoconstriction can be induced by means of adrenalin.

This view, that adrenalin acts on nerve endings, is supported by the observations of Macfie (474), who found that extracts of the adrenal and other tissues are without effect upon the embryonic heart, upon leucocytes, and upon cilia. Again, the work of Brodie and Dixon (138), who find that there are no vasomotor nerves for the pulmonary arterioles, and that adrenin, when perfused through the pulmonary vessels, produces no constriction, is decidedly in favour of the theory that the substance acts upon nerve tissue only.<sup>1</sup>

On the other hand, Boruttau (129) considers that the action is direct on somatic muscle, since it occurs in curarized muscle,<sup>2</sup> and, according to Lewandowsky (458, 460), the dilation of the pupil and other eye effects are produced by a direct action of adrenal extract on the constricted muscle.

<sup>1</sup> See, however, discussion on p. 172.

<sup>2</sup> It does not follow, of course, that, because a curarized muscle cannot be excited through its nerve, therefore the *whole* of the nerve endings are paralyzed.

This was inferred from the fact, referred to above (p. 178), that the extract is still effective after the superior cervical ganglion has been excised and the nerve fibres from it have degenerated. With regard to somatic muscle, Langley (435) is inclined to accept Lewandowsky's view, while in the matter of plain muscle he is content (in the paper of 1901-02) with the generalization that the effect of adrenalin is the same as the effect of exciting the sympathetic nerves supplying the particular tissue (see above, p. 179).

In studies on the action of adrenalin on the bloodvessels of the rabbit's ear Meltzer and Auer (497) showed that section of the sympathetic has a marked effect on the results of intravenous injection of the drug. While on the normal side the constriction of the vessels reaches its maximum in a few seconds, on the side of the section it lasts a very long time, and is very pronounced. Following up the discovery of Lewandowsky (confirmed by Boruttan and Langley), that intravenous injection of adrenalin induces a temporary dilation of the pupil, Meltzer and Auer (499) found that, though subcutaneous injection and conjunctival instillation produce no effect in the normal animal<sup>1</sup> or after section of the cervical sympathetic, yet such administration produces very striking dilation of the pupil after removal of the superior cervical ganglion—that is to say, "the paradoxical effect" is marked in the case of adrenal extract.<sup>2</sup>

These observations were confirmed and extended by Elliott (237), who generalized as follows: "This, then, is true for all the muscles thrown into contraction by adrenalin, that after decentralization—*i. e.*, degenerative section of the preganglionic sympathetic nerves—and still more clearly after denervation (degenerative section of the post-ganglionic sympathetic nerves), they contract in the presence of adrenalin alike with greater irritability and persistence." Elliott concluded as to the localization of the action of adrenalin that the excitation must be due to some substance within the muscle fibres being affected by the drug, and

<sup>1</sup> See, however, Wessely (745).

<sup>2</sup> In a later communication (500) Meltzer and Auer point out an important difference between mammals (rabbits and cats) and the frog. In the latter animal in a normal state, subcutaneous injection or instillation into the conjunctival sac produces in a few minutes a characteristic dilation of the pupil, which may last for hours, so that the frog has become a convenient means of testing adrenal extracts. See also Kahn (386) and Ehrmann (234).

suggested that this substance is present at the "myoneural junction," where it is originally formed.

Schäfer (625) adds a further suggestion—viz., that the formation of this substance, being once started, its amount is also controlled by the sympathetic, and if this control be cut off an inordinate quantity may accumulate, thus increasing the excitability of the isolated muscle fibres. As pointed out by Schäfer, the observations of Macfie (see above, p. 180) prove that the presence of nerve fibres is essential to the original appearance of such hypothetical excitable substance.

These different views do not accord very well together, but the fact that adrenin has functionally a very intimate relation to the sympathetic nervous system is particularly interesting when we remember the accepted origin of the chromaphil tissues.

According to recent observations by Langley, in all cells two constituents at least must be distinguished: (1) Substances concerned with carrying out the chief functions of the cells, such as contraction, secretion, the formation of special metabolic products; and (2) receptive substances, especially liable to change, and capable of setting the chief substance in action. According to this author, the active substance of the adrenals produces its effects by combining with the receptive substance, and not on nerve endings nor the chief substance. So that in this view the controversy as to whether adrenalin acts on muscle itself or on sympathetic nerve endings is compromised by assuming that there is some material in cells originally under control of the sympathetic, which material is specially excited by adrenalin [Langley (436)].

This theory of Langley has not been, however, universally accepted. Lichtwitz and Hirsch (465) and Cardone (160) have quite recently published some evidence which tends to show that after all adrenin acts directly upon the smooth muscle.

Among the other effects of adrenin which have been noted are increase of intra-ocular pressure [Kahn (389)] after intravenous injection, and changes in the structure and function of the kidneys [Schatiloff (630)]. Bardier and Fraenkel (71) and Bardier (68) record a diminution of secretion of urine owing to constriction of renal vessels after the administra-

tion of adrenin. Subsequently the conditions are reversed. Adrenin mydriasis has been employed as a diagnostic sign of increased diffusibility of the cornea [Cords (187)]. Adrenin appears to increase the activity of anæsthetics applied locally to a nerve [Esch (243)].

Cats appear to be peculiarly liable to collapse after intravenous injection of adrenin under light chloroform anæsthesia [Levy (457)]. Full chloroform anæsthesia appears to be absolutely protective. There is probably some unknown condition of the heart under the influence of low percentages of chloroform, which renders it incapable of accommodation to vascular strain.

In the experience of the present writer, also, it has very frequently happened that dogs have been killed by a dose of adrenin (administered intravenously) which it was expected would only be sufficient to produce a moderate rise of blood-pressure. This has occurred with both adrenal extracts and the purified adrenin, and it is not clear that it is dependent on the nature or amount of the anæsthetic employed. The phenomenon seems to depend upon a peculiar idiosyncrasy in some animals, and is comparable to what was found in respect of the general effects produced in various animals by subcutaneous injections (see p. 156).

A large amount of work has been carried out upon the antagonism between adrenin and various other drugs. Only a few of the more recent papers will be referred to. In many respects there appears to be a true antagonistic action between adrenin and calcium chloride, although the latter substance does not hinder the production of adrenin arteriosclerosis [Schrank (638)]. Adrenin is also stated to act as an antidote to poisoning by strychnine, aconitine, and belladonna [Jona (381)]. A pharmacological antagonism is alleged between adrenin and secretin [Gley (317)], while adrenin exercises no action which can be regarded as antagonistic to that of albumoses and of pilocarpine upon the pancreatic and salivary secretions [Gley (318)]. It is stated by Frankl (271) that the chlorides of calcium, barium, magnesium, and potassium can neutralize the mydriatic action of adrenin.<sup>1</sup>

<sup>1</sup> A further paper on the pharmacology of adrenin, in relation to the innervation of the iris, is that of Straub (675).

The table on pp. 186-189, taken from Biedl (105), gives a summary of the chief actions of adrenin and a comparison between these actions and those produced by stimulation of nerves belonging to the sympathetic and autonomic systems :<sup>1</sup>

**M. The Chemical Nature of the Active Substance of the Adrenal Medulla and other Chromaphil Tissues.**

It is one of the greatest triumphs of physiological chemistry that within seven years of the discovery of the powerful effects of extracts of the adrenal medulla by Oliver and Schäfer, the active principle was obtained in crystalline form, and that five years later its composition has been so completely ascertained that it has been synthesized, and the pure active synthetic product can now be obtained from the manufacturing chemists.

In 1856 Vulpian (736, 737) described a powerfully reducing substance in the medulla of the adrenal body. This material was found to give various colour reactions on being oxidized—*e.g.*, with ferric chloride it gave a dark green or blue colour, and with chlorine, bromine, or iodine water or caustic alkalies a rose red. Holm (363), Arnold (48), and Krukenberg (427) attempted, but without success, to isolate the "chromogen" of the gland from a lead precipitate. They all obtained decomposition products. Krukenberg, however, established the important fact that the adrenal chromogen, in regard to certain properties (iron reaction, reducing power, production of a dark coloration with oxidizing agents), corresponds with pyrocatechin. This analogy led Brunner (149) to the false conclusion that the chromogen is identical with pyrocatechin.

Immediately after the publication of the discovery of Oliver and Schäfer, Moore (511) concluded that the active substance is identical with the chromogen described by Vulpian.

Fränkel (267), by treatment of adrenal extracts with alcohol, acetone, and ether, obtained a syrupy preparation of great physiological activity. This was the first claimant to the title of the isolated active principle of the medulla of

<sup>1</sup> This table should be compared with one previously given by Elliott (353).

the adrenal body. It was called "*Sphygmogenin*."<sup>1</sup> Fränkel was also able to show that the chromogen furnishes a benzoyl product insoluble in water, and contains nitrogen in stable combination. This author was the first to express the opinion that the pressor substance is a nitrogenous derivative of orthodihydroxy-benzene. The statement of Mühlmann (520) that from it pyrocatechin could be obtained simply by boiling with hydrochloric acid was refuted by Metzger (503), Abel and Crawford (10), and v. Fürth (284). The last-named observer, on the other hand, showed that by dry distillation of the chromogen a compound is obtained which, as regards its reaction towards iron salts (emerald green coloration, which on the addition of alkali becomes carmine red) and its solubility (in ether, whether out of acid or alkaline solution), corresponds with pyrocatechin.

With a view to the isolation of the extraordinarily unstable and easily oxidizable active substance, v. Fürth (285, 286, 287) extracted with alcohol at a low temperature; then, after getting rid of inactive substances by means of neutral lead acetate, threw down a precipitate with ammoniacal lead hydroxide. By decomposing with sulphuric acid, concentrating the filtrate *in vacuo* and in a stream of carbonic acid gas, extraction of the residue with alcohol, and precipitation with ether, the chromogen was obtained in the form of a slightly pigmented precipitate which was extremely active physiologically.

Turning to account an observation by Hofmeister that by reduction of the adrenal extract with zinc dust in acid solution one could to a certain extent counteract the instability of the chromogen, v. Fürth made use of the following improved process: The adrenals were extracted with dilute zinc sulphate solution, the extracts freed from protein by heating, and treated with excess of ammonia, by which means the chromogen was thrown down as a zinc compound. This was washed, decomposed in a mixture of alcohol and sulphuric acid, the acid filtrate decolorized by means of heating with zinc dust, neutralized with zinc oxide, filtered hot, freed from zinc salts by means of alcohol and ether,

<sup>1</sup> No chemical criteria of the purity of this substance were given. Fränkel did not show that it possessed a constant percentage composition, and no attempt was made to establish even an empirical formula for it.



TABLE OF ACTIONS OF ADRENIN COMPARED WITH THOSE OF STIMULATION OF THE SYMPATHETIC AND THE AUTONOMIC NERVES (BIEDL).

Organs and Tissues.	Action of Adrenin.	Effect of Stimulation of the—			
		Sympathetic Thoraco-lumbar Nerves.	Autonomic Cranial Nerves.	Autonomic Sacral Nerves.	
<b>SMOOTH MUSCLE:</b>					
<i>Alimentary canal:</i> Oesophagus	Relaxation	Relaxation	Contraction and relaxation ( <i>Langley</i> )	Contraction of end portion (birds)	Contraction
Cardiac sphincter	Relaxation	Relaxation	First inhibition, then powerful contraction ( <i>Langley</i> )		
Stomach: Cat, rabbit	Inhibition	Inhibition	Contraction and relaxation ( <i>Beisbridge</i> and <i>Dale</i> )	Variable (?)	Pelvic nerve.
Birds	Inhibition	Inhibition			
Frog	Contraction	Contraction	No action	Contraction	Contraction
Gall-bladder	Relaxation	Relaxation		Relaxation	Relaxation
Bile-duct	Contraction	Contraction		Contraction	Contraction
Small intestine: Mammals	Inhibition	Inhibition		Relaxation (?)	Relaxation (?)
Birds	Contraction	Contraction			
Ileo-caecal sphincter (cat)	Contraction	Contraction			
Colon and rectum	Relaxation	Relaxation			
Recto-coccygeus muscle	Relaxation	Relaxation			
Internal anal sphincter: Rabbit	Relaxation	Relaxation			
Dog and cat	Contraction	Contraction			
Birds	Contraction	Contraction			
<i>Urinary apparatus:</i> Ureter	Contraction	Contraction			
Urinary bladder: Cat and monkey	Relaxation	Relaxation			
Dog and rabbit	Indifferent	Indifferent			
Ferret and goat	Contraction	Contraction			
Frog	Contraction	Contraction			
Urethra	Contraction (?)	Contraction (?)			

<i>Genital apparatus:</i>			
Uterus, Fallopian tubes, vagina:	Contraction	Relaxation and contraction	
Virgin .. .. .		Powerful contraction	
Pregnant .. .. .	Powerful contraction	Contraction	Relaxation (Langley).
Ves. seminales, vasa deferentia..	Contraction	Contraction (stronger)	Relaxation (pelvic nerve).
External genitals:		No action	
Retractor penis muscle	Contraction	Stronger contraction	
Ano-genital muscles .. .. .	Contraction	Contraction	
Tunica dartos (Lieber)	Relaxation	Contraction	
Lungs: Bronchial muscles .. .. .	No action (relaxation?)	No action	Contraction (vagus)
Skin: Arrectores pilorum, Mammals	Weak contraction		
Birds .. .. .	Contraction		
Eyes: Retractor palpebr. tert.	Contraction		Inhibition (abducens nerve) (Lewi and Fröhlich)
Lid muscles .. .. .	Contraction (opening of lid-cleft)	Contraction	
Orbital muscle .. .. .	Contraction (protrusion of the ball)	Contraction	
Pupil: Sphincter iridis .. .. .		Contraction (oculomotor and ciliary nerves)	
Dilatator .. .. .	After elimination of sympathetic inhibition, powerful contraction	(Inhibition) and contraction	
Ciliary muscle .. .. .			Contraction (ciliary nerves)
Pigment cells: Skin (Lieber)	Contraction	Contraction (Gasp)	
Retina (Klett) .. .. .	Contraction		

TABLE OF ACTIONS OF ADRENIN COMPARED WITH THOSE OF STIMULATION OF THE SYMPATHETIC AND THE AUTONOMIC NERVES (BIEDL)—Continued.

Organs and Tissues.	Action of Adrenin.	Effect of Stimulation of the—	
		Sympathetic, Thoracic-Lumbar Nerves.	Autonomic Cranial Nerve. Autonomic Sacral Nerve.
<b>HEART:</b>			
Auricles .. .. .	..	Beat accelerated and strengthened	Inhibition (vagus)
Ventricles: Mammals .. .. .	..	Beat strengthened	No inhibition
Birds ( <i>Elliott</i> ) .. .. .	..	No action	Constriction (?) (vagus)
Reptiles (tortoise, <i>Elliott</i> ) .. .. .	..	Beat strengthened	Dilatation (?) (vagus)
Amphibians .. .. .	..	Beat strengthened	Dilatation (?) (vagus)
Fishes (selachians, <i>Biedl</i> ) .. .. .	..	No action	Dilatation (?) (vagus)
Invertebrates (crab, <i>Elliott</i> ) .. .. .	..	Dilatation	Dilatation (?) (vagus)
Coronary vessels .. .. .	..	Relaxation	Dilatation (?) (vagus)
Isolated strips ( <i>Langendorff</i> ) .. .. .	..	..	..
<b>BLOODVESSELS:</b>			
Of the brains ( <i>Biedl</i> and <i>Reiner</i> ) .. .. .	..	Direct action (Constriction)	Constriction
Of the retina ( <i>Kahn</i> ) .. .. .	..	On intravenous injection, passive dilatation	Constriction
Of buccal mucous membrane .. .. .	..	Constriction ( <i>Elliott</i> )	Dilatation ( <i>Daestre</i> and <i>Morus</i> )
Of lingual mucous membrane and of the salivary glands: .. .. .	..	Constriction	Constriction and dilatation
Of the lungs .. .. .	..	No certain action	..
Of abdominal viscera:			
Spleen .. .. .	..	Constriction	..
Small intestine .. .. .	..	Constriction	..
Rectum .. .. .	..	Elective constriction	..
Kidney .. .. .	..	( <i>Joneacu</i> )	Dilatation (pelvic nerve)

Internal genital organs .. ..	Constriction	Constriction	
External genital organs (vessels of penis) .. ..	Constriction	Constriction	Dilatation (pelvic nerve = <i>Nervus erigens</i> )
Of the skin and the muscles .. ..	Direct action; constriction; intravenous injection; passive dilatation		
<b>GLANDS:</b>			
Lachrymal glands .. ..	Secretion	Secretion	
Mucous glands: Mouth, oesophagus .. ..	Secretion	Secretion	
Salivary glands .. ..	Secretion (sympathetic saliva)	Secretion (sympathetic saliva)	Secretion (chorda tympani) (chorda saliva)
Gastric glands .. ..	Secretion (?) ( <i>Yukawa</i> )	Bile secretion	Secretion (vagus)
Liver .. ..	Scanty bile secretion	Secretion	
Pancreas .. ..	Increased secretion	Secretion (vasodilatation, <i>Biedl, Watterman</i> and <i>Smit</i> )	
Adrenal bodies .. ..	Vasoconstriction and vasodilatation		
Kidneys .. ..	Primary inhibition, then increased secretion ( <i>Hardier</i> and <i>Frankel</i> )		
Sweat glands .. ..	No secretion	Secretion	
Glands of skin and nictitating membrane of frog .. ..	Secretion	Secretion	
Formation of lymph .. ..	Increased (oedema), increased flow from thoracic duct ( <i>Ca-mus</i> )		
Resorption .. ..	Slowed		
<b>METABOLISM:</b>			
Sugar tonus .. ..	Raised (glycosuria)	Raised (glycosuria), diabetic puncture	
Heat tonus .. ..	Raised	Raised, heat puncture	

and finally concentrated. The process was also varied by using ammoniacal lead hydroxide instead of the zinc compound. The amorphous pyrocatechin-like substance obtained by these methods was precipitable from alcoholic solution by means of ether. In the state of solution preserved in sealed tubes it showed considerable stability, and possessed a high degree of physiological activity. A dose of 0.000025 gramme raised the blood-pressure of a rabbit to nearly double its original height. At a later date Abel (7) made a comparison between a preparation obtained by the above lead process and the crystalline *adrenalin* obtained by Takamine's process (*vide infra*). The test was a double one. On the one hand a colorimetric estimation of the iron compound was made, and on the other hand the relative effect upon the blood-pressure was noted, and in neither case was v. Fürth's substance shown to be weaker than that of Takamine.<sup>1</sup> Von Fürth called his substance "*Suprarenin*."

Abel and Crawford (10) converted the pyrocatechin-like substance into a benzoyl compound, and observed after saponification by addition of alkali a smell like that of coniine or pyridin. Furthermore, they made the very important observation that, by distillation of the product with zinc dust in a stream of hydrogen, pyrrol was obtained, and they arrived finally at the conclusion that the active principle of the adrenal medulla belongs to the series of the pyridin bases. This has not been confirmed by subsequent investigation. Moore (512) came to the same conclusion, since he observed that if some adrenal extract be cautiously fused with caustic potash so as to avoid charring, the peculiar odour of pyridin was at once obtained. But, as pointed out by Moore in this relation,<sup>2</sup> it is piperidin, and not pyridin, which has a marked effect upon the blood-pressure. Moore surmised, therefore, that the active substance is a piperidin derivative—*i.e.*, that it contains a hydrogenated ring.

V. Fürth (286, 287) next proceeded to the formation of an iron compound of the active principle. An extract of the glands was made by boiling with acidulated water with

<sup>1</sup> In recognition of this fact the term "*suprarenin*" is still frequently used, especially in Germany, for the active principle of the chromophil tissues.

<sup>2</sup> Previously noted, however, by Tunnicliffe (700).

the addition of zinc dust. The extract was concentrated *in vacuo*, the residue extracted with methyl alcohol, and the solution, after getting rid of inactive substances by means of zinc chloride and acetone, decomposed with chloride of iron and ammonia. The iron compound of the "suprarenin" separated out in the form of a carmine-red flocculent precipitate. The substance was then repeatedly dissolved in dilute ammonia, and precipitated by means of acetone, and the final product was extremely active physiologically, though not yet chemically pure. Analysis indicated that the suprarenin probably contained C 8-9, H 11-13, O 3-4 per cent.

Abel (4, 5, 6) came to essentially different conclusions as to the chemical nature of the active substance. This worker benzoated adrenal extracts after the method of Schotten and Baumann, saponified the purified benzoyl product in the autoclave at a pressure of 3 to 5 atmospheres with dilute sulphuric acid, and precipitated with dilute ammonia or picric acid from the solution so obtained a substance which he called "*Epinephrin*," which he considered was the isolated active principle of the adrenal medulla. It yields picrates and other salts, and is a substance of an alkaloidal nature, having the elementary composition  $C_{17}H_{15}NO_4$ . V. Fürth has shown (286) that Abel's epinephrin is quite a different substance from his own suprarenin, that the former possesses in itself no physiological action, and that whatever physiological effects may be induced by its administration are due to admixture with suprarenin. Epinephrin is also distinguished from suprarenin by its precipitation by means of precipitants of alkaloids (phosphotungstic acid, picric acid, tannic acid, etc.), by zinc chloride, by the absence of reducing power, and the absence of the colour reaction with perchloride of iron. Its separation from suprarenin can conveniently be effected by careful neutralization of the acid solution with very dilute ammonia, by which means the epinephrin separates out as a dark flocculent precipitate easily soluble in excess of ammonia.

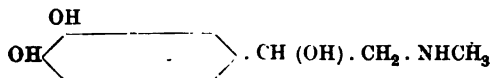
Abel (8) has since shown that epinephrin is to be looked upon as a derivative of suprarenin arising as a result of the treatment with acid in the autoclave. The fact that a methylandol is obtained by fusing epinephrin with potash

must be regarded as of importance in explaining the constitution of suprarenin. Abel has suggested the possibility that by the autoclave treatment a portion of the nitrogen is split off from the suprarenin molecule. This view has been confirmed by v. Fürth (288). Afterwards, however, Abel (9) was inclined to believe that by treatment of the benzoyl product in the autoclave saponification was not complete, and the resulting substance was still a benzoyl product ( $C_{17}H_{15}NO_4$ ); epinephrin would therefore be a monobenzoyl-suprarenin ( $C_6H_5CO$ )  $C_{10}H_{10}NO_3$ ; to suprarenin itself must then be allotted the formula  $C_{10}H_{11}NO_3$ .

The next important step was the production of the active substance in a crystalline form. This was effected by Takamine (688, 689) and Aldrich (35, 36, 37) independently. The method in both cases was the same. Very concentrated adrenal extracts were largely freed from inactive substances by treatment with alcohol, lead acetate, etc.; then the active substance was precipitated in the form of microscopic crystals by the addition of concentrated ammonia. The precipitate was then purified by repeatedly dissolving in acid and reprecipitating with ammonia. The resulting prismatic needles or rhombic plates were those of the purified and isolated active principle—adrenalin.

According to v. Fürth, a careful comparison of the composition and physiological action of adrenalin with those of his suprarenin indicates that they are one and the same substance. He has decomposed the "suprarenin" iron compound with sulphuric acid and thereby obtained "adrenalin" in crystalline form (288).

All the authors quoted have obtained different analytical results and suggested different formulæ. Aldrich suggested from his analysis the formula  $C_9H_{13}NO_3$ , Takamine  $C_{10}H_{15}NO_3$ , and Abel  $C_{10}H_{13}NO_3 + \frac{1}{2}H_2O$ . The empirical formula of Aldrich is now generally accepted, and from the combined researches of v. Fürth, Jowett (384), and Pauly (559), the constitutional formula is regarded as—







would put the relative strengths between 24 : 13 and 30 : 16. Cushny found further that the doses necessary to cause glycosuria are similarly in the proportion of 12 to 18 : 1. The minimal lethal doses as tested by subcutaneous injection appear to bear the same relation. No evidence was obtained suggesting that adrenalin acts elsewhere than on the receptive substances of the sympathetic myoneural junction.

We have seen that the terms "epinephrin," "sphygmogenin," "suprarenin," and "adrenalin" have been applied to the active principle of the chromophil tissues. Other names which have been employed are "hemisine," "paragangline," and "myosthenine." Adrenalin is, however, the term most commonly used ; but it is advisable to adopt a name which has no commercial attachments, and Schäfer suggests "adrenin." This term has been adopted in the present work, and is used where reference is not made to some particular preparation.

As it will be more fully stated below (p. 201), adrenin is widely employed as a drug, and numerous preparations have been placed upon the market, and manufacturing druggists have extensively advertised many forms of the pure product. As pointed out by Schultz (639), the different preparations vary greatly in physiological activity—some, even, being worthless, this being due partly to a lack of care in the process of preparation, and partly to the nature of the container and solvent used in bottling the extract. Schultz narrates that in one instance only 6 grammes of pure adrenalin could be obtained from a sample supposed to contain 19.4 grammes of natural *l*-adrenalin base. He finds that the ratio of physiological activity of the natural *l*-base and the synthetic *dl*-product are to each other as 2 : 3 instead of 1 : 2, according to Cushny.

The physiological activity of all adrenin-like bodies can be assayed by the blood-pressure method and their efficiency expressed in terms of pure adrenin base. Hence, if one has two solutions, a known adrenin solution, 1 c.c. of which contains *a* grammes of the base, and an unknown containing a certain amount, *y*, of vasoconstrictor exciting substance, they can readily be checked against each other by the blood-pressure method. Whichever solution is the stronger

can be diluted until 1 c.c. injections of it cause the same rise of blood-pressure as the other, and finally their relative activity calculated by the following equation :

$$\frac{x \text{ adrenin base}}{y \text{ vasoconstrictor excitant}} = \text{relative activity.}$$

Schultz (640) has investigated a series of specimens of adrenin sold under different names by various firms. Of the seven different brands of "epinephrin" examined, only three possessed an activity that equalled the standard. The other solutions varied anywhere from 3.75 to 71 per cent. of the required activity. Some of the solutions were worthless, and perhaps even dangerous. Certain solutions, though showing a high degree of activity upon opening the original package, quickly deteriorated in spite of the extra precautions taken to guard against conditions known to further this process. This author remarks that, on the other hand, some of the preparations now upon the market made by American firms are of the very highest quality.<sup>1</sup>

It has recently been shown [Ewins (253)] that the iodine reaction [Vulpian (736, 737)], the mercuric chloride reaction [rose-red colour, Comessatti (185, 186)], and the bi-iodate reaction [Fränkel and Allers (272)], [Krauss (423, 424)], are due wholly or in part to oxidation. Potassium persulphate was found by Ewins to have a similar oxidizing action upon adrenin, giving a characteristic red colour. This reaction is stated to have advantages over those mentioned above both in sensitiveness and in being readily obtained with crude extracts of chromaphil tissues. The Comessatti reaction appears to be due to the oxidation of adrenin by such oxidizing agents as mercuric chloride, silver nitrate, or platinic chloride under the catalytic influence of salts of metals with "weak" acids (*i.e.*, salts which are hydrolytically dissociated by water). The reaction may be compared with the results which have been obtained in the investigation of certain "laccases."<sup>2</sup> The characteristic colour reactions of adrenin are given by

<sup>1</sup> See also Cameron (154), Crawford (190), Gunn and Harrison (344), Houghton (365, 366, 367, 368), Hunt (370), Schultz (641), Sollmann and Brown (654).

<sup>2</sup> Euler and Bolin (251).

certain other closely related bases—namely, by (a) the amino base, corresponding to adrenin; (b) dihydroxyphenylethylamine and the corresponding methyl, ethyl, and propyl-amino bases; (c) amino-aceto pyrogallol. The bases of the type amino-aceto catechol do not give these reactions [Ewins (253)].

The physiological action of adrenin, an action simulating that of the true sympathetic nervous system, is possessed also by a large series of amines, the simplest being primary fatty amines. Barger and Dale (72) describe all such amines and their action as "sympathomimetic." They find, as the result of a careful investigation, that the more nearly the structure of an amine approaches to that of adrenin, the more intense and the more specific is its sympathomimetic action. All the chemical products which possess this specific action are primary and secondary amines. The quaternary amines corresponding to the aromatic members of the series have an action closely similar to that of nicotine. There are two optimum conditions of chemical structure in which the action is most pronounced. The first is a benzene ring with a side-chain of two carbon atoms, the terminal one bearing the amino group. The second is the presence of two phenolic hydroxyls in the 3 : 4 position relative to the side-chain; when these are present an alcoholic hydroxyl still further intensifies the activity. A phenolic hydroxyl in the 1 position does not increase the activity.

Harold, Nierenstein, and Roaf (353) also ascribe the main factor in the "sympathomimetic action" to the presence of an amine group, separated from the benzene ring by a carbon chain.<sup>1</sup>

As a practical result of these investigations 3 : 4 dihydroxyphenylethylmethylamine, one of the most active of the sympathomimetic amines, has been put upon the market and is advertised under the name of "epinine" ("the synthetic hæmostatic"). It is claimed that this product "possesses the characteristic physiological action of the extract of the suprarenal gland, but is superior in

<sup>1</sup> Other papers on the chemistry of the adrenals (chromaphil tissues) are: Lépinos (450), Okerblom (534, 535), Jacoby (376), Croftan (196), Jones and Whipple (382), Meyer (505), Bertrand (94, 95, 96), Roger (615).

that its purity is chemically controlled, its stability is greater, and the rise of blood-pressure it produces is more prolonged."

#### N. The Origin of Adrenin in the Body.

Three suggestions have been made as to the origin of adrenin in the body. Boruttau (560) believes that the waste products of muscular metabolism are converted into adrenin. This view appears to be based upon results obtained by Boruttau and Langlois upon frogs whose adrenal bodies had been removed, and which were benefited by injection of adrenal extracts. Similar views are held by Battelli and Roatta. The theory would imply the formation of adrenin from some such substance as creatin. This is the least probable of the three suggestions.

Abelous, Soulié, and Toujan (17-23) are of the opinion that adrenin is manufactured in the cortex from tryptophane.

Halle (345) has suggested that one of the substances from which adrenin is formed in the organism may be tyrosin, and has brought forward some evidence for this view. He points out that adrenin might be produced from tyrosin by (1) introduction of a hydroxyl group into the benzene ring; (2) elimination of  $\text{CO}_2$  from an amino-acid to form an amine; (3) the methylation of nitrogen; (4) the introduction of a hydroxyl group into an aliphatic chain. He states that when two portions of emulsion of fresh ox or pig adrenal were taken, to one of them tyrosin being added, both being kept under aseptic conditions for six days in an incubator, the sample containing the tyrosin was found to have from 14 to 33 per cent. more adrenin than the control.

Gessard (302) imagines a relationship between tyrosin and adrenin, because both substances become pigmented in a similar manner by the action of tyrosinase.

The theoretical speculations of Halle would appear to be open to criticism, as pointed out by Ewins and Laidlaw (254). Moreover, the last-named observers were unable to confirm Halle's experimental results. The matter is by no means settled, and, although the hypothesis that adrenin may be derived from tyrosin is not supported by the evidence

before us, yet it would be rash to dismiss this substance from consideration as one of the possible precursors of adrenin in the animal economy.

Ewins and Laidlaw were further unable to find any evidence that adrenin may be formed by ferment activity from the closely related bases parahydroxyphenylethylamine and dihydroxyphenylethylmethylamine.<sup>1</sup>

#### O. The Mode of Disposal of Adrenin in the Body.

It was found by Oliver and Schäfer (539) that adrenal extracts not only produce a contraction or increase of tone in cardiac and vascular muscle, but that frogs which had received a subcutaneous injection show an increased power of contraction of the skeletal muscles on stimulation of their nerves. This also applies to mammals, and the effect lasts for some time after the effects upon the vascular system have disappeared. Oliver and Schäfer, therefore, came to the conclusion that the active substance is probably taken up by, and remains for a time stored within, muscle, and that this may in a measure account for its disappearance from the blood. It is not excreted by the urine, nor is it at once reabsorbed by the capsules. Its ultimate disappearance is probably due to a process of oxidation in the tissues. Oxidation of the active principle does not occur, according to Oliver and Schäfer, in the blood.

Langlois (444) found that the rate of destruction is proportional to the activity of the tissues generally. Thus, in hibernating or cooled animals, the process of destruction is slow. According to the author, destruction of the active principle occurs throughout the whole body, though chiefly in the liver. The injection into the mesenteric vein of a dose sufficient to raise the blood-pressure considerably, if injected into the general circulation, produces no effect. Athanasiu and Langlois (54) also found that Fränkel's "sphygmogenin," when injected, is destroyed in the liver. It was also stated that adrenal extracts are rendered inactive by ozone or other oxidizing agent.

Livon (467) thought that the active principle is destroyed in the muscles.

<sup>1</sup> See also Funk (291).

The experiments of Embden and v. Fürth (240) show that digestion of adrenin for two hours with normal blood, laky blood, or blood-serum, causes a considerable destruction of the active principle. On the other hand, addition of muscle, liver, or lung extract to the blood (as also perfusion experiments) causes a less destruction or none at all. Comparative experiments with weak alkaline solutions teach that the destruction in the blood is essentially due to the alkali, and the hindrance to destruction in the organs to the formation of acid. Nevertheless, these authors are not of opinion that the rapid cessation of action on the vessels is to be attributed to a rapid oxidation;<sup>1</sup> they consider, rather, that the contraction of the muscles of the bloodvessels ceases so soon as the concentration of the adrenal solution by diffusion or dilution with the blood and tissue fluids sinks to a certain level. They quote an observation of Boehm (117), that barium salts on intravenous injection cause a rise of blood-pressure similar to that produced by adrenin.

The disappearance of the effect of a dose of adrenin has been attributed to the alkalinity of the blood. Thus, Kretschmer (426) finds that if this is diminished by the administration of acids, the effect of the drug upon the blood-pressure is prolonged. It is even affirmed [Miller (508)] that the active substance does not disappear from the blood, and that the blood of a rabbit which has received a dose of adrenin will cause the typical rise of blood-pressure if injected into another rabbit, although the effects upon the first animal may have disappeared.

The subject of the inactivation of adrenalin and one of the sympathomimetic amines *in vitro* and *in vivo* has recently been investigated by Cramer (189), who reports that a solution of adrenalin can be completely inactivated by allowing it to stand with a dilute solution of formaldehyde for a few minutes. "Epinine" (see p. 196), under similar circumstances, also becomes inactivated. Pituitrin and the other hormones are not so inactivated by formaldehyde. It is suggested that the inactivation of adrenin in the organism is brought about not by a process of oxidation, but by a combination with a product of metabolism pro-

<sup>1</sup> So, also Siegel (648).

duced by the cells on which adrenalin has acted, and that it is a process similar to the reaction *in vitro* previously described.<sup>1</sup>

#### P. The Proteins, Lipoids, etc., of the Adrenal Bodies.

There is nothing very special or characteristic in the *proteins* which can be extracted from the adrenal bodies. Nabarro (527) investigated the proteins derivable from the adrenal bodies of the calf. These he extracted with 5 per cent.  $MgSO_4$  solution, and found the albumins, globulins, and nucleo-proteins which are found in animal tissues generally.

The *extractives* and salts, moreover, do not call for any special mention.

The subject of the occurrence of *choline* in animal tissues has already been sufficiently dealt with (p. 26 *et seq.*). It is probable that we are justified in considering that whatever choline may be present in the adrenal bodies is of no special functional significance.

The *lipoid substances* contained in the cortex of the adrenal body are probably of considerable importance, and their chemical nature may yet reveal the secretory function of the cells of this part of the adrenal gland. Their presence in the cells has been known to histologists and morphologists for a long time, but attempts to deal systematically with their chemistry are of recent date. So far as they are involved in a treatment of the microscopic structure of the adrenal cortex, they will be discussed in a later section of this work (p. 226). At this stage it will be desirable to state what is known of these substances from a more purely chemical standpoint.

According to Fränkel (269, 270), the different organs of the body contain different lipoids, which are characteristic for each particular organ. The difference between the lipoids of various organs on the one hand and the lipoids of the same organ in different groups of animals vary both qualitatively and quantitatively.

<sup>1</sup> Ceviddali and Leoncini (165, 166, 167, 168) state that in cases of sudden death the adrenals contain more adrenin than in cases of gradual death. This observation, if it can be confirmed, may be of considerable medico-legal importance.

Biedl (105) has devoted special attention to the lipoids of the adrenal bodies of the pig. He finds that the glands contain 74.61 per cent. water, and 25.39 per cent. of dry substance. Of this dry substance, 61.12 per cent. consists of protein, and 38.88 per cent. lipoids and extractives. It is pointed out that since the extracts were made from the whole gland, the cortex must contain a much greater proportion of lipoids. In order to prove this point definitely it is proposed to investigate the inter-renal body (which consists of cortex only) in the Elasmobranch fishes.

Thus we see that the adrenals must be placed among the organs richest in lipoids, since a third of the total dry substance is made up of these materials. Among the definite chemical compounds recognized by Biedl in the adrenal extracts are cholesterinpalmitate [ $C_{27}H_{45}O$  ( $C_{16}H_{31}O$ )], the cholesterin ester of carnaubic acid [ $C_{27}H_{45}O$  ( $C_{24}H_{47}O$ )], and kephalin.

According to Biedl, it appears probable that the cholesterin esters are specific for each particular organ and perhaps for each particular species, but not that they are to be regarded as a definite secretory product of the gland.

#### Q. The Medical and Surgical Employment of Adrenal Preparations.

After the observation of Oliver (583), that an artery in the frog's mesentery is contracted by adrenal extract to such an extent that blood ceases to be driven through it, Oliver and Schäfer began to use the extract as a styptic in their experimental operations; its application for this and similar purposes is now general. Schäfer (625) states that in epistaxis he himself early had an opportunity of verifying its styptic property.

*Surgical Employment of Adrenin alone or combined with other Drugs.*—Braun (134, 135, 136) found that a subcutaneous injection of adrenalin solution (1 in 10,000) produces a bloodless condition of the tissues quite as readily as the method of bandaging or freezing. Next, adrenalin was combined with cocaine for subcutaneous injection, and it was found that the effect of the cocaine was increased and lasted for a longer time. A combination of adrenalin with eucaine was also found to be very beneficial. It is



stated that the toxic effects of cocaine are to a certain extent neutralized by the simultaneous employment of adrenalin.<sup>1</sup>

Braun has made extensive use of this method, employing the following solution : 100 c.c. of a 0.05 per cent. solution of cocaine hydrochloride, using 6 per cent. sodium chloride solution as a solvent, to which 3 to 5 drops of adrenalin hydrochloride (1 in 1,000) are added ; the dose is 50 c.c. to 100 c.c. The operation may be performed ten minutes after the injection. The lower part of the rectum may thus be rendered insensitve, and operations for fistulæ or hæmorrhoids, or dilatation of the sphincter, may be performed in a painless manner. The method may also be used for excision of a piece of rib, for operations on the scalp, for removal of sebaceous cysts, for amputation of a finger, etc.

Major operations under spinal anæsthesia produced by 1 in 2,000 adrenalin solution in conjunction with 0.0075 to 0.015 gramme cocaine, have also been performed without ill-effects [Dönitz (214)].

Honigmann (364) uses  $\beta$ -eucaine instead of cocaine for local anæsthesia. The use of cocaine and adrenalin combined is also recommended by Foisy (264, 265), Perthes, and Meisel (564).

Barker (73) strongly recommends  $\beta$ -eucaine instead of cocaine. His experience leads him to the conclusion that for ordinary surgical work the following solution answers well :

Distilled water	..	..	..	..	..	100 c.c.
$\beta$ -eucaine	..	..	..	..	..	0.2 gramme.
Sodium chloride	..	..	..	..	..	0.8 gramme.
1 pro mille adrenalin chloride solution	..	..	..	..	..	ix.

The actual strength of adrenalin in this solution is one in two hundred thousand (1 : 200,000). On production of local and regional anæsthesia by means of this fluid, Barker has performed the following operations with the most satisfactory results : (1) Amputation through the knee-joint for gangrene of the foot due to diseased arteries and diabetes ; (2) abdominal section and opening of the stomach and jejunum in search of a source of severe bleeding (not found) ; (3) removal of a cyst of the thyroid ; (4) Bassini's radical cure of inguinal hernia ; (5) removal of a silver wire from round the patella.

<sup>1</sup> Novocaine is now frequently employed.

Equally favourable results are recorded by other surgeons.

Local anæsthesia produced by the combined use of adrenalin and cocaine, or  $\beta$ -eucaine, has also been employed in gynæcological operations besides those involving abdominal section. The method has been found useful in operations for prolapsus uteri and plastic operations on the vagina; owing to the anæmia produced by these solutions, they were serviceable also in amputation of the cervix.

*Application of Adrenal Preparations to the Conjunctiva and other Mucous Surfaces.*—Oliver found that a congested and inflamed conjunctiva is at once rendered pallid under the influence of adrenal extract. The use of adrenal derivatives in ophthalmological operations and examinations has been attended with great advances in this department. In various operations on the eye the field of operation may be kept free from blood by the use of adrenalin solution, 1 to 50 drops of a solution of the strength of 1 in 5,000, or 1 in 10,000. Darier (204) recommends the following solution for the purposes of removal of a foreign body from the eye, cauterization, etc.: 10 drops of a solution of adrenalin hydrochloride (1 in 1,000); cocaine hydrochloride, 0.1 gramme; distilled sterilized water, 10 grammes. Bates (84) independently extolled the virtues of adrenal extracts in the treatment of diseases of the eye. He found that they whiten the conjunctiva in trachoma, conjunctivitis, keratitis, iritis, and other conditions. An eye with a foreign body on the cornea is whitened. During operations on the ocular muscles, tenotomy, and advancement, the extract whitens the eyeball; the astringent effect is temporary, and there is no subsequent congestion. Bates says: "It is the only remedy of which I know that is purely an astringent. It is the ideal hæmostatic. It acts by contracting the muscle of the small arteries until the lumen is occluded and a coagulum is formed inside the artery." Again, "Within the limits of its sphere of activity there is absolutely no other substance which can take its place." The local action of adrenin is very evanescent, and the application has to be repeated every four or five minutes.

In diseases of the nose and throat adrenal preparations have found a useful application. Newcome, in 1899 (529),

gave a good review of the subject. Adrenal extract was first used in diseases of the nose by Bates. Later Swain (682), Mullen (521), Lermitte (451), and Peters (565) recommended this drug.

Ledermann (448) advised a glycerin-watery solution.

Cohen (183) found that adrenal extracts controlled the symptoms of hay fever in his own case.

Yearsley (771) was one of the first in England to employ adrenal preparations for rhinological purposes. The extract was used in some forty cases as an aid to diagnosis, and the marked ischæmia it caused was most useful in revealing causes of obstruction. Yearsley also made trial of the drug as a hæmostatic with good results, also in hay fever, epistaxis, and paroxysmal sneezing and rhinorrhœa.

Kyle (431) and Rosenberg (618) have also successfully employed adrenal preparations in diseases of the nose.<sup>1</sup>

Läwen (432) employs a solution of cocaine and adrenalin for the painless extraction of teeth.

In bronchial asthma adrenalin applied to the nasal membrane has been used for some years. Kaplan (395) has more recently employed subcutaneous or intravenous injection (5 to 15 minims of the 1 in 1,000 solution). Miller (508) reports favourably on the drug administered in one of these ways for bronchial asthma; the relief was considerable, but in no cases could he observe any curative effect. On the other hand, there were no untoward results. It is not known how the beneficial effect is produced in these cases—perhaps it is due to inhibition of the bronchial musculature. But Miller is inclined to think that the results point to the pathology of bronchial asthma being due to a hyperæmia of the bronchial membrane.

*Use of Adrenal Preparations in Diseases of the Bladder.*—Braun (137) recommends a mixture of adrenalin and cocaine for injection into the bladder preparatory to a cystoscopic examination. So also Harris (354). V. Frisch (274) also found adrenalin useful in catheterization for urethral stricture. Kirch (399) found that injection subcutaneously, every two hours, of four doses of 1 c.c. of adrenalin solution (1 in 1,000) relieved bleeding occurring

<sup>1</sup> See also Baéza (63), Mignon (507), Escat (244), Bukofzer (150), Hecht (356), Douglass (218).

in the urinary tract. Moresco (518) found adrenalin useful in atony of the bladder.

*The Use of Adrenal Preparations and of Adrenin in Hæmorrhages.*—Clinical experience has shown that when hæmorrhage occurs from a surface to which adrenalin may be applied, relief is prompt, and in the large majority of cases, lasting. The drug then finds ready application in epistaxis, bleeding from granulating wounds, from the atonic uterus, and in cases of deep tears of the cervix uteri, and in many other similar cases.

Schäfer (625) believes that when adrenin is given by the mouth there is "very distinct evidence of vascular constriction, for bleeding from internal parts, such as the stomach, intestine, bladder, and uterus, and even the bleeding of post-partum hæmorrhages, may thereby be effectually controlled." The explanation offered by Schäfer is that injured vessels are more susceptible to the extract and react to a slight excess of it in the blood more readily than do normal vessels. But Miller (508) considers that as regards vessels not accessible to local applications the constrictor action of adrenin is more than counterbalanced by the sudden increase of general blood-pressure. He states that in rabbits he has observed that in a wound the vessels that have stopped oozing often start bleeding after an intravenous injection of adrenalin. In pulmonary hæmorrhage, he thinks, there is the additional danger of possible absence of vasoconstriction, and therefore the bleeding might increase by having a condition of dilated vessels with increased pressure. Schäfer replies to this that administration by the mouth does not perceptibly raise the systemic blood-pressure, and that, nevertheless, there is considerable clinical evidence that internal hæmorrhages, when not too profuse nor coming from large vessels, may be brought under control by oral administration, especially if, as he suggests, the extract has a greater effect upon injured vessels.

The question just discussed, naturally, is of great import in relation to the treatment of hæmoptysis. Batty Shaw (647) inclines to the view that hypodermic or oral administration of adrenin can have little effect upon bleeding occurring from destructive tuberculous disease of the lungs, and he

attaches comparatively little importance to the clinical reports which so far have been published, and in which it is impossible to say that the good results were not due to other factors.<sup>1</sup>

Quite recently Wiggers (762) has investigated the value of adrenalin in inaccessible internal hæmorrhages. He concludes that large doses of the drug (0.05 to 0.1 milligramme) cause a short preliminary increase of hæmorrhage followed quickly by a decrease or cessation of bleeding. On account of the great preliminary loss of blood, they are always contra-indicated. Small doses (0.01 to 0.025 milligramme) cause little or no preliminary increase, but shorten the course of hæmorrhage. As they save the red blood cells in every way, they are therapeutically desirable. Continuous intravenous injection of weak solutions maintains a slight elevation of pressure, and hæmorrhage is simultaneously checked. This can also be accomplished by intramuscular injections. Adrenalin is not indicated in all intestinal hæmorrhages. The condition of the blood-pressure is the criterion for its use. In hæmorrhages of short duration, when the pressure has not fallen to any extent, a judicious dose of nitrites proves of more benefit than adrenalin. When the bleeding has been profuse, however, and a low pressure already exists, it becomes vital that hæmorrhage should be checked without further reduction of pressure. Adrenalin finds its use in this field. The use of adrenalin should always be closely followed by blood-pressure observation. A dose sure to be below the safety limit should first be tried and the pressure carefully estimated. If no rise occurs, gradually increasing doses may be injected until a slight elevation of pressure is present, in which case we may be certain that enough has been introduced to affect hæmorrhage, and at least no significant preliminary increase has resulted.

*Adrenin in Cardio-Vascular Conditions.*—In cardiovascular conditions adrenin is most distinctly indicated when there is marked vasodilation and the heart muscle is in good condition [Miller (508)]. These indications are

<sup>1</sup> Some of these favourable reports are contained in the following papers: Voigt (734), Hedley (358), Bowen (131), Renon and Loutè (602), Souques and Morel (657), Macdonald (473), Ducanson (227), Le Noir (530).

present in chloral-poisoning, shock, and asphyxia. Gottlieb<sup>1</sup> (321) pointed out that when a rabbit has received increasing doses of chloral until the heart comes to a standstill, adrenal extract will start the heart beating and maintain it for from twenty to thirty minutes. He considers that adrenalin is superior to digitalis for this purpose. Crile (193, 194) strongly advocates the use of adrenalin in "surgical shock," and although good results have been stated to accrue from its employment in ether-poisoning (Miller, Schäfer), yet, according to Schäfer and Scharlieb (629), it is of little avail to restore a heart paralyzed by chloroform.

In the cardiac insufficiency of diphtheria—in which disease, as Elliott and Tuckett (239) have shown, there is a deficiency of chromogen in the adrenal medulla—Gottlieb has reported that adrenin administered intravenously is of temporary benefit. The same applies to phosphorus-poisoning. Schäfer suggests that administration by the mouth or subcutaneously, having a slower effect, might be beneficial in such cases. Rolleston (617) has recently discussed the value of adrenalin in such cases as the cardiac failure of diphtheria, and lays stress, as others have done, upon the possibility that the increase of the peripheral resistance may give the failing heart ventricle more work to do. He states, however, that he has for some time been in the habit of giving adrenalin by the mouth in cases of pneumonia in adults, and in broncho-pneumonia in children. In these cases it appears to prevent cardiac failure, and has not given rise to any bad symptoms such as œdema of the lungs. He mentions, however, the possibility that such administration of adrenalin may give rise to arterial degeneration.

Roy-Teissier (619) treated two patients suffering from cardiac weakness and emphysema with 0.5 milligramme daily of adrenalin or 0.05 milligramme every two hours. Improvement was prompt. Adrenal extract is stated to be useful in functional disorders of the heart associated with lowered arterial tension. In certain cases, therefore, it may be indicated in migraine and neurasthenia, where these disorders are associated with a low blood-pressure.

Kauert (397) has quite recently recommended the use of

<sup>1</sup> See also Biedl (98).

synthetic suprarenin in medicine. He reports that it is useful in cases of vasomotor paralysis, and may be used both therapeutically and prophylactically. The dose is from 1 to 6 milligrammes subcutaneously,  $\frac{1}{4}$  to 1 milligramme intravenously. The drug is contra-indicated in organic heart disease, nephritis, and arterio-sclerosis with high blood-pressure.

*Adrenal Preparations in Addison's Disease.*—The clinical evidence as to the value of adrenal extracts and preparations in the treatment of Addison's disease is very conflicting. A cure can, indeed, scarcely be expected by treatment directed towards remedying adrenal inadequacy, for the reason that this inadequacy is only one result of a tubercular or malignant disease, or a definite atrophy of the gland. Shaw (647) points out that there are several other reasons why such treatment should fail. Among these he mentions our ignorance of the functions of the cortex of the gland and the difficulty of securing the absorption of an adequate amount of adrenalin.

The beneficial results which have been alleged are to be found chiefly in diminishing the weakness and sense of lassitude. Langlois (439), Mahe (477), Chauffard (171), and Dupaigne (228) report encouraging results. Numerous cases have since been treated with varying degrees of success.<sup>1</sup>

Rolleston (617) refers to cases of chronic adrenal inadequacy, or "Addisonism." Boinet (126) recommends adrenalin in these cases. Various diseased conditions, such as cyclical albuminuria, neurasthenia, with low blood-pressure, purpura [Loeper (469, 470, 471)], status lymphaticus, and hæmophilia, have been attributed to adrenal inadequacy, and hence adrenalin has been recommended. But in these cases, as in those of Addison's disease, it seems very unwise to administer simply the pressor substance extracted from the medulla. In the present state of our knowledge it would be far more desirable to give either the fresh whole gland or extracts prepared from the whole gland, both cortex and medulla. The pigmentation in Addison's disease has probably never been experimentally induced, and

<sup>1</sup> Richter (606), Korczynski (418), Kinnicut (398), Deeks (205), Boinet (125), Adams (26). In some cases the results of treatment have been distinctly bad. Thus Picardt (576) records marked increase of protein metabolism and rapidly diminished body strength and weight. The patient soon died.

certainly has never been satisfactorily explained, and we are in the dark as to whether this, one of the most striking symptoms of the disease, is due to a lesion of cortex or of medulla, or is due to damage to both.

We have seen that the results of treatment of Addison's disease by means of adrenal gland substance are—as compared with the effects of thyroid treatment in myxœdema—distinctly disappointing, though it may be that in some instances good results have been obtained. Dr. Byrom Bramwell, who regards the symptoms of Addison's disease as partly due to glandular inadequacy, and partly the result of irritation of the sympathetic in the neighbourhood of the adrenal bodies, explains the failure of the extract in some cases by supposing that in these instances there are adhesions to the sympathetic plexus and irritation of it; while the cases which react satisfactorily to the extract are those in which there is only glandular inactivity or inadequacy.

Rolleston (617) says: "It should be remembered that the medulla alone contains the active physiological principle, the cortex appearing to be inert, and that the extract is at present largely made from the whole gland, and not, as would be physiologically more correct, from the medulla alone. This must lead to a certain amount of uncertainty as to the amount of active principle contained in any pill or tabloid." It will be gathered from what has been said above (p. 128) that it appears to the present writer that it is far from certain that it would be "physiologically more correct" to give extracts made from medulla only, or to give, as would probably be suggested at the present time, pure adrenin. It seems safer, in view of our ignorance of the precise pathology of the disease, to give an extract made from the whole gland, or, better still, if administration by the mouth be considered advisable, the fresh minced gland. Because the medulla is the only part which yields a powerful active substance to extracts, we must not assume that it is the only part concerned in Addison's disease. In relation to this subject reference may be made to the observations of Bittorf (p. 128).

*Various Applications of Adrenal Preparations and of Adrenin.*—Barr (74, 75) found that after withdrawal of fluid from the pleural cavity of a patient suffering from



carcinoma of the lung, the fluid did not accumulate again after the introduction of adrenalin. The same applies to tuberculous pleurisy, tuberculous and malignant peritonitis, and to ascites due to cirrhosis. The method was, after removal of the fluid, to inject 40 to 60 minims of adrenalin chloride, 1 in 1,000. In ascites the success was not so great as in the other cases.

Plant and Steele (579) report good results in cirrhosis of the liver and pleural effusion, and state their belief that the injection of adrenalin chloride is strongly indicated in all cases of serous effusion when simple tapping does not effect a cure. The empirical results obtained by Barr and others are explained by the experiments of Exner (255), and Meltzer and Auer (498, 502). Exner found after experimental injection of adrenalin that absorption of strychnine and physostigmine is delayed, and so the life of the animal may be saved. This was confirmed by Meltzer and Auer, who also showed that fluorescein transfused from the blood into the peritoneum much more slowly in animals that had previously received adrenalin intravenously. It has also been demonstrated that intraperitoneal injection of adrenalin will lessen the tendency of transudation into the peritoneal cavity, after excessive transfusion of normal salt solution.

It has been stated [Carnot and Slavu (164)] that in dogs injection of adrenalin exercises a beneficial effect on the process of consolidation after fracture of bones.

*Mode of Administration of Adrenal Preparations.*—It is well to recall that adrenal extracts were first administered by subcutaneous injection. But since Oliver and Schäfer reported that the activity of the gland is not impaired *in vitro* by pepsin and hydrochloric acid,<sup>1</sup> it has become customary to give it by the mouth. Raw sheep's adrenal bodies have been given, and a tincture has also been employed, but most usually a dried extract is employed in the form of a pill. In addition to these modes of exhibition all the various forms of the active substance adrenin have been used from time to time.

Some years ago the present writer failed to observe any physiological effects upon dogs, cats, and rabbits of feeding with the adrenal bodies of the sheep [Vincent (729)], and the

<sup>1</sup> See, however, Miller (508).

administration of large doses of extracts (in some cases made from medulla only) failed to produce any noticeable rise of blood-pressure in the human subject.<sup>1</sup> But Grünbaum (332) states that adrenal extract, although when administered by the mouth it ordinarily fails to produce elevation of blood-pressure, will bring about this effect in cases of Addison's disease. However this may be, the most certain method by which to obtain any definite pharmacodynamical effects is that of subcutaneous, intramuscular, or intravenous injection. The intravenous method should be employed in all cases of extreme emergency, such as ether-poisoning and heart failure in diphtheria.

Miller urges that adrenin ought to be employed with great care in all patients with suspected arterial degeneration, and in elderly people. The danger of causing glycosuria in the human subject does not appear to be great.<sup>2</sup>

#### R. Theories as to the Function or Functions of the Adrenal Bodies.

No good result would accrue from a study of the ancient history of views which have been held as to the functions of the adrenal bodies. Some account of the older references to these bodies is given on p. 90.

Our scientific knowledge of the adrenal bodies may be said to date from the year 1855, when Addison published his famous work (28). The known facts about the organs in question are, very briefly stated, as follows: Disease of the glands gives rise to a characteristic train of symptoms, among which are pigmentation of the skin and extreme muscular weakness. Extirpation of both adrenal bodies is a very dangerous operation, and, according to the majority of investigators, invariably leads to death. Extracts of the medullary portion of the body are toxic when administered to an animal subcutaneously, intramuscularly, or intravenously, among the symptoms being glycosuria and degeneration of the arteries. Intravenous injection produces a powerful effect upon the heart and bloodvessels, and

<sup>1</sup> D'Amato (45) has also shown that very large doses given in this manner to rabbits do not increase pressure, although they may cause arterial degeneration (see also p. 175 *et seq.*).

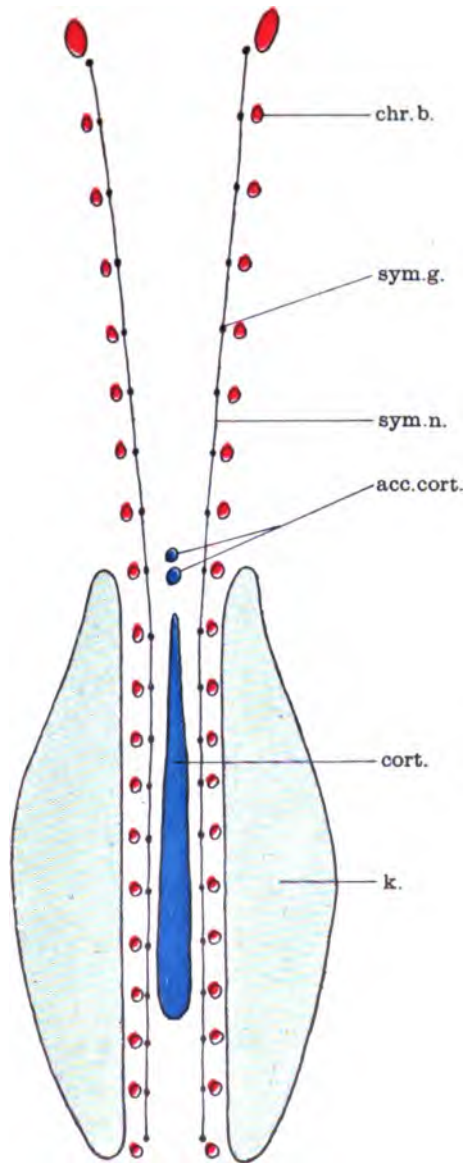
<sup>2</sup> Other papers on the medical and surgical uses of adrenin are: Königstein (404, 405), Carnot and Jossierand (162), Cramer (188).

is chiefly manifested by a very marked rise of the arterial blood-pressure. The general pharmacodynamical effects are strikingly similar to those brought about by a stimulation of the sympathetic nervous system ; these physiological or pharmacological effects are obtained only by administering extracts of the medulla, the cortex being inactive.

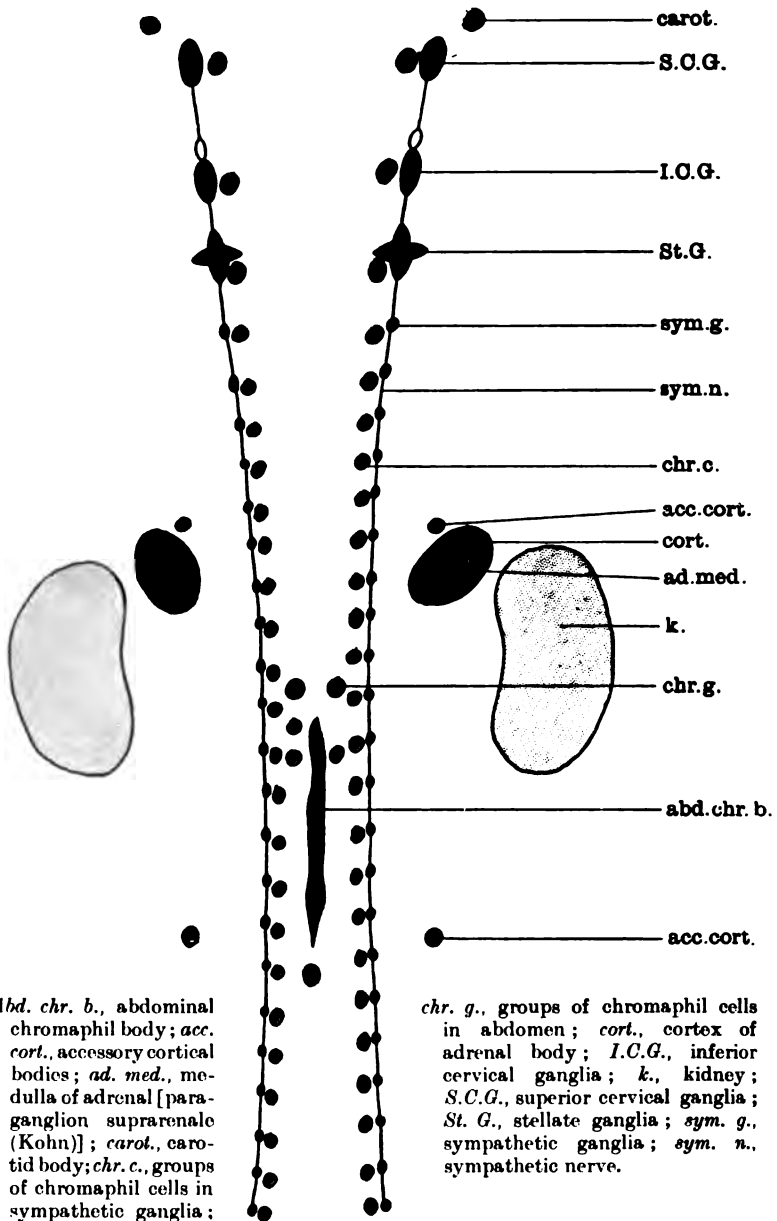
Comparative anatomy and comparative physiology reveal the fact that the medulla of the adrenal body is not the only representative in the body of the tissue which forms it (chromaphil tissue) ; there are numerous scattered bodies of the same nature in close relation to the sympathetic ganglia and nerves in different regions of the body. In lower vertebrate animals the medulla (chromaphil bodies) and cortex (inter-renal bodies) form two separate and independent systems, having no anatomical (and, so far as we know, no physiological) relationship to each other. Indeed, strictly speaking, the medullary substance is not part of the adrenal body at all, but simply an accumulation of the chromaphil tissue which has arisen from the sympathetic in a certain region of the body, and has insinuated itself into the adrenal proper, or what we call the "cortex." This, at any rate, is the view of Kohn and several other recent investigators.

In discussing the function or functions of the adrenal bodies these facts of comparative anatomy must not for a moment be lost sight of. The ultimate question which we have to solve is, from the standpoint of comparative physiology, not so much what is the function of the adrenal body or of its two constituent portions, but what are the functions respectively of the inter-renal system (cortical system) and the chromaphil system (medullary system), which are, as we have seen, separate and distinct in Elasmobranch fishes (Figs. 45, 46) ? It is difficult to say whether we ought to expect that these functions should be of a kindred nature, or in any way related to each other, in the case of the mammals. There certainly would be no *a priori* reason for suspecting the existence of any such relationship in the Elasmobranch fishes, but we cannot overlook the fact that phylogenetically and ontogenetically the two tissues become attracted, so to speak, to each other, and finally in the adult mammal form a single compound organ. One cannot escape from the suspicion that the coming together may have some

*Acc. cort.*, accessory cortical bodies; *chr. b.*, chromaphil bodies (paired suprarenals) paraganglia (Kohn); *cort.*, cortex of adrenal body (interrenal body); *k.*, kidney; *sym. g.*, sympathetic ganglia; *sym. n.*, sympathetic nerve.



**FIGS. 38 and 45.**—Diagram of the adrenal representatives in Elasmobranch fishes, showing the cortical gland (inter-renal body) and the medullary glands (chromaphil bodies, “paired suprarenals”) in relation to the sympathetic and the kidneys. The cortical elements are coloured blue, while the medullary constituents are put in in red.



FIGS. 39 and 46.—Diagram of the adrenal constituents and outstanding "cortical" and "medullary" (chromaphil) bodies in the mammal, showing the adrenal bodies, the chromaphil cells of the sympathetic and the abdominal chromaphil body ("accessory cortical adrenals") in relation to the sympathetic and the kidneys.

significance affecting the functions of the gland as a whole. We are, however, at present completely in the dark as to any functional correlation between the two constituents. It is possible, moreover, that cortex and medulla have separate and distinct functions; at any rate, all the accurate knowledge which we possess and nearly all our most plausible hypotheses have reference to the medulla of the organ, and this notwithstanding the fact that the cortex is larger than the medulla, and more distinctly glandular in type and appearance.

1. *Theories as to the Function of the Medulla.*

Prior to the discovery of the active principle of the medulla of the adrenal body, some authors considered that the gland has an excretory function. Thus, MacMunn (475) found hæmochromogen in the gland, and especially in the medulla, and drew the conclusion that in the adrenals a downward metamorphosis of worn-out pigments—hæmoglobins and histohæmatins—is taking place, and that the function of these organs is to pick out of the circulation these worn-out or effete colouring matters with their accompanying proteins. Others considered that the waste products of muscular metabolism are eliminated by the glands. Still others attributed a blood-destroying function to the gland [Auld (58, 59)]. But since the discovery of the pressor principle by Oliver and Schäfer (537), the excretory theory has almost entirely been replaced by that of secretion—internal secretion.

It is now generally admitted that most, if not all, of the recognized effects produced by the administration of adrenal extracts are to be ascribed to the adrenin which is contained in them. Three questions immediately arise: Is adrenin to be looked upon as the product of the secretory activity of the medulla of the glands? Is it actually poured out into the blood-stream? Supposing these questions to be answered in the affirmative, then what is the use of this internal secretion—this hormone—in the animal economy?

Kohn (410, and other papers), from morphological considerations, is opposed to the view that the chromophil tissues have an internal secretion. He is certainly justified in insisting that we have no right, simply because adrenin

has certain pharmacodynamical effects, therefore to assume, without further definite evidence, that it is one of the functions of chromaphil tissues to pour out this substance into the blood-stream in order that it may produce such effects upon certain tissues of the body. He considers that the cells forming the medulla of the adrenal body and the chromaphil tissues elsewhere are not "epithelial," and therefore cannot secrete.<sup>1</sup>

The present writer has replied to some of these arguments on previous occasions. Some years ago it was pointed out (730) that the active substance of the adrenal medulla is of a very exceptional and extraordinary character, and is not to be classed with the less active bodies found in extracts of organs and tissues generally. Again, it was stated that the medulla of the adrenal body is not a mass of chromaphil cells of irregular shape and indefinite arrangement, but an organ arranged in the form of definite columns of cells, with intervening blood-spaces—in fact, a "gland." It was thus thought that it is extremely probable that the adrenal medulla is constantly secreting into the blood-stream an active material which produces beneficial effects upon the muscular tissues of the body. Again, more recently (731) a careful comparative study of the chromaphil tissues in general, and the adrenal medulla in particular, has led to the conclusion that the latter is probably to be regarded as a specialized development of the former (see p. 118).

Lewandowsky (459, 461) also is opposed to the "internal secretion" theory of the adrenal bodies. The effects of extracts are, according to his view, purely pharmacodynamic, and have no relation to the physiology of the organs. This applies to the effects upon both the blood-pressure and the smooth muscle of the skin.

Considerable evidence has, however, been accumulated that adrenin is secreted through the adrenal veins into the general blood-stream. It has been stated by Cybulski (684, 685, 687), and by Langlois (442), and Biedl (100), that the blood of the adrenal vein contains a sufficient amount of the active principle of adrenal extract to produce marked rise of blood-pressure when intravenously injected. Schäfer (627), however, has been unable to confirm this. Salvioli

<sup>1</sup> See also Wiesel (752).

and Pezzolini (621) state that the blood from the adrenal vein acts like adrenal extract, but weakly. Battelli (78) reports that he has been able to detect adrenin in the blood of normal animals, and records changes in the amount present according to the state of muscular activity of the animal [Battelli and Roatta (80)].

Ehrmann (233), basing his investigations upon the discovery of Lewandowsky (458, 459), and relying upon the observations of Meltzer and Auer (500) that frogs, after adrenalin injection, show a maximum dilatation of the pupil, worked out a method for the estimation of adrenin. He used the enucleated frog's eye, as recommended by Meltzer and Auer, and measured the amount and rapidity of widening of the pupil on placing the eye in adrenin solution. By this method it could be shown that the blood coming from the adrenal bodies contains the active substance, adrenin, and Ehrmann concludes that it passes into the blood as a physiological secretion. This act of secretion is constant. Pilocarpin and atropin lead to no marked increase or diminution. In diphtheria intoxication it is somewhat increased. Raising or lowering the blood-pressure has no effect on its amount, which varies considerably in different animals.<sup>1</sup> According to Ehrmann, the rabbit pours into its adrenal veins adrenin in a concentration of between 1 : 1,000,000 and 1 : 10,000,000. There is a parallelism between the amount secreted and the sensibility of the animal to the action of the substance.

Waterman and Boddaert, however (741), have shown that the mydriatic action on the enucleated frog's eye is not absolutely specific for adrenin. Gautier (295) says that the solutions employed must be faintly acid, since dilute alkali in sodium chloride solution gives by itself a positive result. Schultz (641) says that the time taken for a certain degree of widening is of more value than the extent of total dilation. The method is now considered by Meltzer (496) to be untrustworthy, as the amount of adrenin necessary to produce

<sup>1</sup> Eichler (235) finds that the serum of nephrectomized animals and patients with renal disease has a mydriatic effect. Dein (206) finds a mydriatic substance in the urine under various conditions, but does not think that this is necessarily adrenin.

For an account of variations in the amount of adrenin in the blood in different pathological conditions, see Salzer and Wilenko (622).



an action upon the frog's eye varies not only in different frogs, but even in the two eyes of the same frog. Trendelenberg (697) now uses the method of perfusion through the vessels of the hind-limb of the frog. Ritchie and Bruce (609), using the bichromate coloration and the blood-pressure testing, have recently reported (contrarily to Ehrmann) that in diphtheritic toxæmia in guinea-pigs there is complete exhaustion of all adrenin from the medulla of the adrenal bodies.

Watermann and Smit (742) employed the method of Fischer (261), which was modified from that of Boek and Hoffmann (118), and Külz (429).<sup>1</sup> This consists in injecting hypertonic solutions into the auricular vein, and noting the occurrence of glycosuria. It was found that this, like the diabetic puncture, also renders the serum mydriatic. The authors consider that these experiments show that adrenin stimulates the sympathetic. In their view also the sympathetic may be stimulated by means of thyroid material, and, on the other hand, stimulation of the sympathetic leads to increased secretion of the thyroid. They look upon Minkowski's pancreatic diabetes as negative pancreas and positive adrenal diabetes.

An elaborate series of metabolism experiments by Eppinger, Falta, and Rudinger (241, 242) seems to point to a definite internal secretion on the part of the adrenal medulla, or rather of the whole chromophil system, and a functional relationship between adrenal body, thyroid, and pancreas through the medium of the sympathetic nervous system. A relationship between pancreas and adrenal body in regard to hyperglycæmia is indicated by the experiments of Zuelzer, Dorhn, and Mayer (776). Ritzmann (610)<sup>2</sup> has shown that the degree of glycosuria depends on the quantity of adrenin present in the blood at any given moment. But the quantitative result of this observer cannot be regarded as correct, since it has been proved by Underhill (703) that the glycosuria obtained by Ritzmann with small doses of adrenin, intravenously administered, was dependent on the use of urethane as the anæsthetic. Adrenin introduced in very dilute solutions (1 : 500,000 to 1 : 125,000) fails to

<sup>1</sup> See also two recent important papers by Skima (651) and Waterman (740).

<sup>2</sup> See also Straub (676) and Pollak (591).

induce glycosuria in the normal rabbit. On the other hand, when the animal is under the influence of urethane narcosis, these dilute adrenin solutions are a sufficient stimulus for the production of glycosuria. It seems, then, that urethane renders a rabbit unusually sensitive to the glycosuria-inducing action of adrenalin. The subcutaneous administration of adrenin in a dilution of 1 : 1,000 to normal rabbits is far more efficacious in causing glycosuria than the same quantity of adrenin introduced intravenously in much greater dilution. The same quantity of adrenalin injected subcutaneously at different periods into the same animal under constant conditions causes the appearance in the urine of variable quantities of sugar [Underhill (703)].

Underhill and Fine (705) have discovered that subcutaneous administration of hydrazine is capable of preventing the appearance of sugar in the urine of dogs from which the pancreas has been removed. They suggest that hydrazine has an action upon sugar metabolism entirely similar to that exerted by the internal secretion of the pancreas. According to this idea, injections of hydrazine cause hypoglycæmia by increasing the efficiency of the pancreatic secretion or by augmenting its output. They find definitely that the secretion of adrenin is not notably inhibited by hydrazine.

As a working hypothesis, the authors make use of the scheme of interaction between the pancreas and the adrenal bodies given on next page.

Ringer (607) has brought forward some results which confirm the work of Straub and Ritzmann, which indicates that adrenalin, by its constricting effect on the blood vessels, produces anæmia of the tissues, resulting in imperfect oxidation, and this anæmia is followed by the conversion of glycogen into dextrose, by hyperglycæmia, and consequently by glycosuria.

In 1891 Jacobi (375) described nerves branching from the splanchnics, and supplying the adrenal bodies. The same observer, in his experiments on the nervous functions of the adrenals, without, of course, having any knowledge of the pressor effects of extracts, reports that in two experiments stimulation of the gland itself produced a rise of blood-pressure. But Apolant (47), in a series of more than thirty experiments upon rabbits, could obtain no such result.

THE DUCTLESS GLANDS

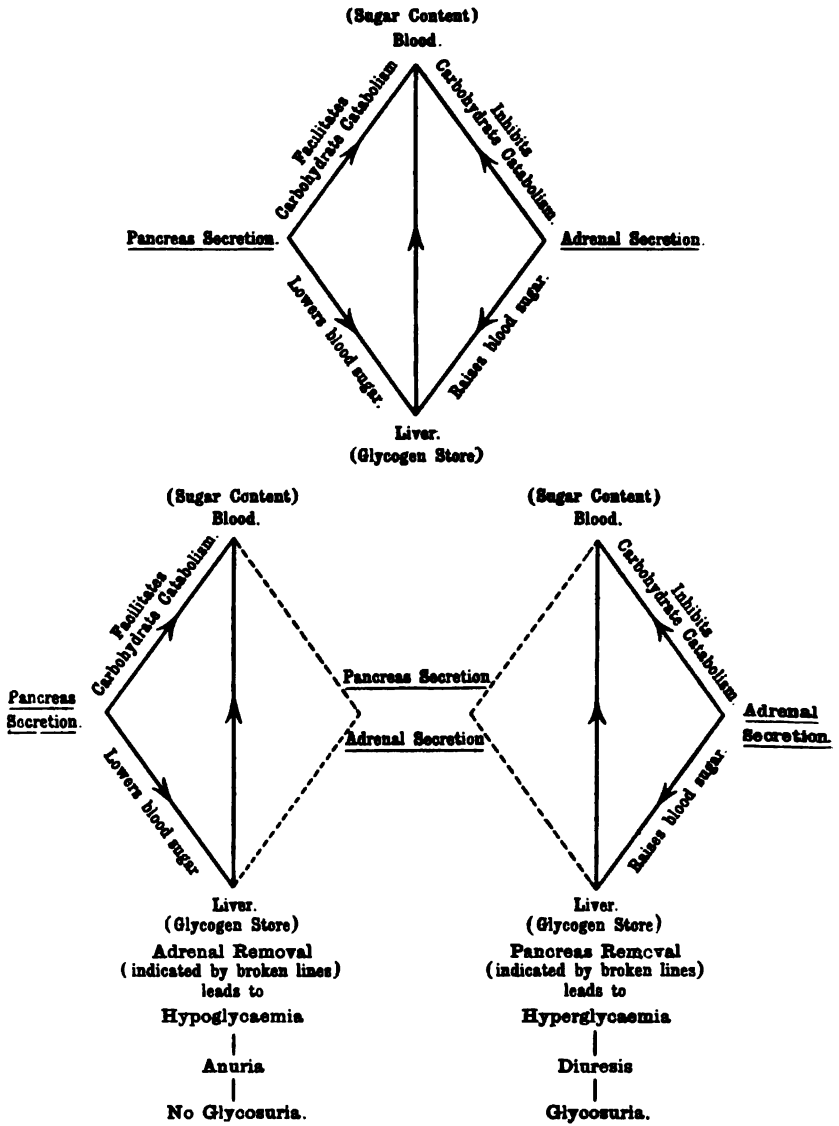


Diagram indicating influence of the organs on the metabolism of carbohydrate (Underhill and Fine).

Biedl (100) found that stimulation of the splanchnics or the ramus suprarenalis gives rise to vasodilation, and suggested that this is accompanied by increased secretion from the gland. We must consider, however, the latter result open to question, as no test of the active principle was made, but only a study of changes in certain granules in the blood of the adrenal vein (*vide infra*).

More definite results were obtained by Dreyer (222), who records that the physiological action of the blood from the adrenal vein during splanchnic stimulation is greater than that of the same blood under normal conditions. He looks upon the splanchnic as a true secretory nerve for the adrenal body.

Have we good grounds for believing that the constant secretion of adrenin into the blood-stream and its action upon the sympathetically innervated vascular muscle is an important factor in the maintenance of the normal blood-pressure? If this be really the case, it ought to be possible by tying or clamping the veins issuing from the glands to keep down the blood-pressure at a low level during the period of clamping or tying, and to allow it to reach its normal level on releasing the clamp or the ligature. Such a result has been definitely recorded by Strehl and Weiss (677), who extirpated the adrenal body on one side, and found that when a clamp was put upon the adrenal vein of the other side the blood-pressure immediately fell, and rose again when the clamp was released. Their experiments were performed upon rabbits. They give a tracing which shows a very marked depression during the period of the clamping of the vein. This tracing has been reproduced by Boruttau (130).

Kretschmer (425) finds that if adrenalin solution is injected intravenously into rabbits each new dose produces a rise of pressure, and between the doses the pressure falls to normal owing to the rapid destruction of adrenalin in the body. For this reason repeated injections cannot keep up the blood-pressure, but *continuous* injection *can* do so. The action on the blood-pressure lasts just so long as there is any adrenalin in the blood. According to Kretschmer, the continuous internal secretion of adrenalin from the adrenal bodies is probably of significance for the maintenance of

the normal vascular tone. If, as *in vitro*, the destruction of adrenalin in the body is dependent on the amount of alkali present, then should intravenous injection of alkali cause a lowering of blood-pressure due to a breaking down of the continuous supply of adrenalin. A lengthening of the action of adrenalin is in fact produced experimentally by a simultaneous injection of nitric acid.

At the suggestion of the present writer, the experiment of Strehl and Weiss has been repeated by Young and Lehmann (772, 773). In their experiments an attempt was made upon dogs to dam back any secretion which the glands may pour into the blood-stream, and after an interval to remove the obstruction and allow the accumulated adrenin to flow into the general circulation. A cannula was inserted into the carotid artery, the adrenal glands were exposed through an abdominal incision, and a double ligature passed beneath the organ on each side; the ligatures were tied on each side of the gland above the vein, so as to form two pedicles. The ligatures were left in place for from ten to thirty minutes, and then released, and the tracing continued. Out of eight experiments, there was no effect on the blood-pressure in three; in two there was a slight rise after releasing the ligatures; in the remaining three there was a decided rise of pressure (similar to that which follows the injection of the extract), lasting about three minutes. In one case the effect was repeated by tightening the ligatures a second time, and again releasing them. After tightening the ligatures, the pressure fell but little and very gradually.

The results of these experiments, though not very conclusive, would seem to point to a secretion of adrenin which becomes manifest after the veins of the adrenal body have been temporarily closed (Fig. 47).

In regard to the question as to the use of this secretion in the economy, the most usually accepted theory is that it helps to maintain the tone of muscular structures innervated by the sympathetic nervous system, and in particular the muscular wall of the bloodvessels. Thus the secretion would constitute one of the chief accessory factors which help to maintain the normal blood-pressure. The experiments of Strehl and Weiss strongly support this view, but so far as I

am aware have never been confirmed. Young and Lehmann were unable to detect any appreciable fall of blood-pressure during the period that the adrenal veins were ligatured off, though there might be a temporary rise when the ligatures were released. Dr. Young informs the present writer that he has repeated these experiments, and finds that even after the lapse of several hours, with the blood from the adrenal bodies absolutely excluded from the circulation, there is no appreciable fall of blood-pressure. One would not perhaps expect that the fall would be immediate and sudden, or follow very rapidly upon the application of a clamp or ligature to the adrenal veins; but if the presence of adrenin in the circulation is in reality an important factor in maintaining the blood-pressure, one certainly would expect that there would be an appreciable lowering of the pressure within a few hours. It seems possible that the results obtained by Strehl and Weiss were due to other causes than the clamping of the adrenal veins.

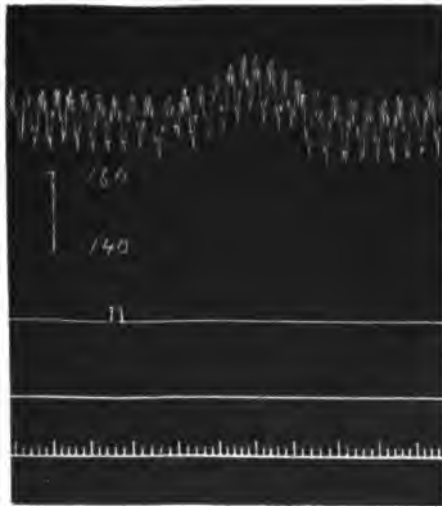


FIG. 47.—This tracing shows the rise of blood-pressure due to release of pressure on adrenal vein. The vein had been compressed for some time, and was released at the point signalled (Gardner and Gunn).

The subject has been recently reinvestigated by Asher (53) and Tscheboksaroff (699). Asher performed his experiments upon rabbits. All the arteries coming off from the abdominal aorta and supplying the viscera, with the exception of those running to the adrenal bodies, were ligatured, and then all the abdominal organs, excepting the liver and the adrenal bodies, were extirpated. The blood was squeezed out of the veins, and the portal vein tied off. Electrodes were then placed under the two splanchnic nerves, the spinal cord was cut across high up, and artificial respira-

tion carried out. The blood-pressure was recorded from the carotid or the femoral artery.

Stimulation of the splanchnic nerves gave rise to a marked rise of blood-pressure, and continuous stimulation produced a long-continued elevation of pressure. The rise did not occur if the adrenal veins were tied.

Tscheboksaroff has reached the same conclusions as Dreyer did—viz., that the great splanchnic nerve in dogs is the true secretory nerve of the adrenal body, and that its stimulation leads to an increase of the adrenin which is found in the venous blood. Section or ligature of this nerve diminishes the amount of adrenin in the blood.<sup>1</sup>

In an article written three years ago the present writer was compelled to express the opinion that the whole matter required renewed investigation. The work of Asher and Tscheboksaroff has been a most important contribution to our knowledge, but it is even yet too early to declare the matter settled.

A very interesting contribution to the subject of the internal secretion of the adrenal bodies has been made by Cannon and de la Paz (158, 159). They point out that, according to the researches of Dreyer, Asher, and Tscheboksaroff, the adrenal secretion is under control of the thoracolumbar autonomic (sympathetic) system. They further call attention to the fact that the phenomena of a major emotional exhibition in an animal indicate the dominance of sympathetic impulses. When, for example, a cat becomes frightened, the pupils dilate, the stomach and intestines are inhibited, the heart beats rapidly, the hairs of the back and tail stand erect—all signs of nervous discharges along sympathetic paths. The authors put to the test the suggestion that the adrenal glands share in the widespread subjugation of the viscera by sympathetic control.

The inhibition of contraction in strips of longitudinal intestinal muscle was used as a physiological test.<sup>2</sup> Blood

<sup>1</sup> Popielski (594) attempts to explain the results obtained by Asher and Tscheboksaroff as being due to vasodilation of the adrenal body, and a washing out of adrenin from the gland.

<sup>2</sup> The authors discuss the various methods of testing for adrenin. The frog-eye method of Meltzer (500) and Ehrmann (233) did not give sufficiently striking results. Strips of ox artery, employed by Meyer (506), though highly sensitive, did not seem serviceable because of Schlayer's (633) discovery that the method is less efficient when used with foreign blood. The uterus method

was obtained from a cat when quiet, and again after the animal was excited by the presence of a barking dog. After an initial shortening the strip contracted rhythmically in blood from a quiet animal. In no instance did such blood produce inhibition. On the other hand, blood taken from animals after the emotional disturbance showed more or less promptly the typical relaxing effect. The effect was obtained in blood from the inferior vena cava near the liver. The authors believe that the effect was due to secretion on the part of the adrenal glands, and they offer a further suggestion that the persistence of the emotional state after the exciting object has disappeared may be in part due to an autogenous continuance of adrenal secretion.<sup>1</sup>

A number of histological observations have been recorded, which point to an active secretion on the part of the adrenal medulla. Manasse (478) described brown masses in the bloodvessels of the adrenal body, and small highly refractive, colourless granules in the adrenal vein of the dog, and Gottschau (323, 325) and Biedl (100) have found in blood taken from the adrenal vein of the rabbit a considerable number of highly refractive granules.

Carlier (161) investigated the adrenal of a hedgehog, and described in the medullary cells deeply staining granules of varying size. These he found also in the lumina of the venous sinuses either singly or in clumps, and states that they could be observed in different stages of elimination from the cells. Canalis (156) had previously described granules in the cells of the medulla, and this had been confirmed by Pfaundler (571). Stilling (669) records that in "hunger" frogs the medullary cells are vacuolated, and take on the bichromate reaction in an irregular fashion. In summer frogs there is a distinct reduction in the amount of the medullary substance.

Hultgren and Anderson (369) give a description of characteristic granules in the medullary cells and in the

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requires several hours (Fränkel, 208). So they finally decided upon the longitudinal intestinal muscle (Magnus, 476). One of the chief advantages of this preparation is that it responds by relaxing. This is very important, for other substances in blood than adrenin—*e.g.*, CO<sub>2</sub>—will cause smooth muscle to contract, whereas known substances evoking relaxation of smooth muscle are few and unusual in blood (Grützner, 333).

<sup>1</sup> Two recent contributions to the physiology of the adrenal secretion will be found in the papers of Battelli and Stern (82), and Torrini (696).



blood of the adrenal vein.<sup>1</sup> They believe that they observed the passage of these through the endothelium of the bloodvessels. Srdinko (659, 662) mentions finely granular masses in the blood spaces, and Lydia Félicine (258, 259, 260) describes in the rabbit, cat, dog, field-mouse, and other animals, sharply defined spaces between the medullary cells, which she regards as intercellular canals. These communicate with blood spaces, and sometimes it may be observed that not only the medullary vessels, but also the lacunæ and the intercellular spaces are filled with fine, darkly staining particles. But the authoress cannot be sure that these are in fact particles of the secreted substance, though she concludes that "the medullary substance of the adrenal body is a gland with an internal secretion."

The particles described by Canalis and Pfaundler were probably, according to Ciaccio (175), centrosomes. The last-named author is strongly inclined to the view that, while the cortex destroys the toxic products of metabolism, the medulla elaborates a substance essential to the economy. Ciaccio (172) also describes pericellular canaliculi, which he considers are intimately related to the processes of secretion. In a later communication (177) the same author describes specific granules in the medullary cells, and these of two kinds: the one having a special affinity for the salts of chromic acid—the chromaphil granules; the other having a special affinity for perchloride of iron.

Recently Stoerk and v. Haberer (672) have stated that the characteristic granules of the protoplasm of the adrenal medulla are not cast out into the lumina of the vessels, but they represent structural units which are possibly to be regarded as the seats of chemical action whose products are to be looked upon as the true secretory materials of the medullary cells, which materials pass into the blood by some such process as diffusion. The fluid secretory product is the true bearer of the chromaphil reaction of the medullary cells, the granules having the reaction only in their secretory phase, when they are just forming the chromaphil substance. The fluid secretion can be recognized intracellularly (in both the protoplasm and the nucleus), and extracellularly (in

<sup>1</sup> Mulon (522), by means of their micro-chemical reactions, identifies these with adrenin.

admixture with the serum of the capillary and venous blood). Besides the typical fine granules of the medullary protoplasm there are coarse structures which occur on the side of the cells turned towards the vessels, and which reveal a different staining reaction from the granules. The capillaries are everywhere bounded by endothelium between the blood and the medullary cells.

Thus it would appear that there is considerable evidence both physiological and histological that the adrenal medulla is, in fact, an internally secreting gland, and that adrenin is the product of its secretion. Assuming this view to be correct, we have next to inquire whether adrenin, in carrying out its normal functions in the body, acts directly upon the sympathetically innervated tissues, or whether it acts in some other more indirect or roundabout manner. Boruttau (130) believes that the function of the adrenal medulla is to render harmless the poisonous products of muscular activity, and render them serviceable for the regulation or the nourishment and innervation of the whole motor apparatus. He appears to be of the opinion that the waste products of muscular metabolism are, in fact, converted into adrenin. Thus he combines the antitoxic theory with that of internal secretion. Langlois holds similar views.

Clinicians and pathologists have now very generally adopted the internal secretion theory of the adrenal medulla, and the chromaphil or "hypertensive" system generally. Thus, Rolleston (617) discusses the possible pathological relations of the internal secretion, and divides these into (1) Alteration in quantity—(a) absence, (b) diminution, and (c) excess; and (2) alteration in quality. There is no need to pursue this subject further.<sup>1</sup>

<sup>1</sup> The following additional papers on the physiology of the adrenal bodies may be consulted: Charrin (168, 169), Radziejewski (598), Battelli (76), and other papers.

Nowicki (532) states that in nephritis the function of the adrenal bodies is increased by reason of a stimulus from the kidneys. The changes in the heart and bloodvessels in kidney disease are, according to this author, the result of hypersecretion of the adrenals.

The function of the chromaphil tissues is first of all hindered by chloroform narcosis and subsequently exaggerated (Marchetti, 481).

2. *Theories as to the Function of the Adrenal Cortex.*

We cannot at the present time allocate any definite function to the cortical portion of the adrenal body, though there can be little doubt that it exercises a very important influence upon the economy. The cortex is larger than the medulla, and is composed of epithelial cells, the appearance and microscopical structure of which suggests a high degree of secretory activity. Moreover, as we have seen (p. 149), there are some reasons for thinking that the cortex is of more importance for the maintenance of life than the medulla.

There are some observations which point to functional changes in the cortical cells. Thus, Stilling (669) finds in summer frogs special elements which he calls "summer cells." These are pear-shaped, stain well with eosin, and possess a nucleus and several nucleoli. The cell body is distinctly granular. In the peripheral part of the cortex mitotic figures are to be observed in them. These Stilling considers are elements *sui generis*, which partly disappear in the autumn and partly lose their characteristic granules, and so are no longer to be recognized. He considers that the summer cells are not connected with the better nutrition in summer, but are closely related to the reproductive function.

The presence of fatty or fat-like substances in the cortical cells has been known for a long time, and has already been referred to from the chemical standpoint (p. 200). They appear to have been first described by Ecker (230). The earlier observers referred to them definitely as fat droplets and fat granules. Kölliker (402) calls attention to differences in the amount of the cortical fat in different classes of animals. The human being has a moderate amount.

Moers (510) and Arnold (49) noted that the highly refractive cortical granules were insoluble in alkalies and in acetic acid. This observation led v. Brunn (148) to question their fatty nature; so also Braun (132) and Gottchau (323, 324, 326).

Rabl (597) investigated the micro-chemical reactions of the cortical cells in birds. He showed that the cortical granules are soluble in alcohol, ether, and chloroform, turn black with osmic acid, and red with alkanna. While, however, fat after treatment with osmic acid is insoluble in

chloroform and oil of bergamot, the cortical granules are soluble in these reagents as well as in xylol. For this reason Rabl considers them only as "fat-like" bodies. These observations were found to be true also of the cortical granules of the horse and the dog [Pflaundler (571)]. Alexander (38), however, states the cortical granules do not stain black with osmic acid, but only take on a brownish tinge; therefore, they must consist of some substance other than fat.

Kaiserling (393), in 1895, reported that a large part of the granules in question are doubly refracting. Orgler (454) concluded that the particles are not fat, but are related to myelin.

Hultgren and Andersson (369) suggested that the granules may be lecithin; but they made no test for phosphorus.

The granules are present in embryonic life, and, according to Plečnik (580), are not to be regarded as representing a fatty degeneration. In the medullary cells in the embryo there are granules which blacken with osmic acid, but these are not abundant, and at the fifth year granules are not present in all medullary cells. Now we find more and more cells which stain black with a clear centre, and after puberty these ring-shaped granules are alone present. After this time any solid granules in the cells show that they really belong to the cortex. Adrenal fat is different from other fat. In the external part of the cortex there are hollow spaces which are often lined with a layer of flat cells or ordinary cortical cells; these are best seen shortly before birth, and are absent in adults.

According to Bernard and Bigart (88), the cortex produces lecithin and pigment. It contains cells with compact (dark) protoplasm, and cells with less compact (light) protoplasm. In the formation of the lecithin, fat-like droplets arise in the cells, and the process appears to progress from the periphery to the centre of the gland. In the pigment formation vacuoles occur in the cells and become filled with fluid. This first occurs in the centre of the cells. Then the pigment appears in the form of granules at the border of the vacuolated part of the cells.

Bernard, Bigart, and Labbé (89) concluded that what Bernard and Bigart called "labile fat" is lecithin or a

mixture of lecithins. They made an estimation on the one hand of the total fat by extraction with ether and alcohol, and, on the other hand, the total quantity of phosphorus contained in the adrenal bodies, and found that the ratio of phosphorized fat to the total fat is 45.3 : 100 in the horse, 48.8 : 100 in the sheep, 52.7 : 100 in the rabbit. The phosphorized fat constitutes 6.77 per cent. of the organs in the horse; in man the ratio of the lecithin to the total fat is 13.1 : 100; the lecithin amounts to 2.08 per cent. of the total weight. According to these authors, the lipoids are increased after muscular labour.

Babes (61) believes that the pigment of the zona reticularis arises from the lipochrome of the fatty layer. When the organ is very rich in fat, this is deposited in crystalline, doubly refracting structures resembling protagon in their reactions. Orgler (545) is of opinion that they are of the nature of myelin.

It is by no means clear that these lipid (phosphorized fat) granules represent the actual secretion of the adrenal cortex. Nor, if such were the case, is it possible at the present time to suggest any reasonable theory as to their function. (See, however, p. 321.)

*Ciaccio's Method for the Demonstration of Lipoids.*

Ciaccio (179, 180, 181) claims that the lipoids in any tissue may be distinguished from the neutral fats by the following histological method: (1) Fixation for twenty-four to forty-eight hours in the following fluid:

Five per cent. pot. bichrom.	..	..	..	..	100 c.c.
Formalin	..	..	..	..	20 c.c.
Acetic acid	..	..	..	..	5 c.c.

(2) Five to eight days in potassium bichromate solution, 3 per cent. (3) Running water, twenty-four hours. (4) Alcohol, twenty-four hours. (5) Absolute alcohol, two hours. (6) Xylol. (7) Paraffin.

The sections are stained with a saturated solution of Sudan III. in 80 per cent. alcohol.

According to Ciaccio, the droplets in the tissues shown by this method consist of lecithin and other lipoids.

Bell (86) has shown, however, that potassium chromate acts upon droplets of neutral fat in the tissues as well as upon the lipoids. It is certain that some lipoids, such as cholesterolin, fatty acid mixtures, cerebroside, etc., are much more readily chromated than neutral fat. But the size of the droplet of neutral fat is a factor of great importance. A small droplet of triolein is completely chromated in the same time that is required to chromate a large lipid droplet. Ciaccio's technique is, however, a valuable method for the study of the fatty substances in the tissues, though it gives only a rough distinction between neutral fats and lipoids (Bell, 86).

See also Aschoff (51), Kasarinoff (396), Kaiserling (392), and Pclósew (502). Other references are given in Bell's paper.

Mulon (524) is of the opinion that in the adrenal cortex a complex lecithalbumin, elaborated by the activity of mitochondria, is poured into the blood-stream. This lecithalbumin he regards as the internal secretion of the adrenal cortex.

There are three principal views as to the function of the cortex—namely, that it has to do with (1) growth and development, especially of the reproductive organs; (2) the neutralizing of toxic substances; (3) the internal secretion of the medulla.

(1) Tumours or hypertrophies of the adrenal body have sometimes been found to be associated with precocious development of the reproductive organs [Wooley (769), Bullock and Sequeira (151)]. Enlargement of the adrenal bodies has been noted during œstrus and pregnancy [Guiseyæ (340)]. There is a striking resemblance between the cells of the adrenal cortex and those of the corpus luteum. This is specially emphasized by Mulon (523), who, from observations on guinea-pigs, goes so far as to speak of the corpus luteum of pregnancy as a temporary cortical adrenal body.

Linser (466) has recorded the case of a giant with a huge adrenal growth, and Scudder (643) has put forward some evidence to show that malignant growths of the cortex tend to produce metastases in bone. Quest (596) finds changes in the adrenals in rachitis.

(2) The theory that the cortex has the power of neutralizing toxic substances has presented itself in two principal forms: (a) That the gland destroys the poisonous products of body metabolism, especially those arising from muscular activity. This is the theory of auto-intoxication, put forward by Abelous and Langlois (12-16 and 438), and was originally applied to the whole gland before the active principle of the medullary chromaphil tissue was discovered. But a modification of the view is now held by Borutttau and Langlois to apply to the secretion of adrenin by the chromaphil cells. (b) That the cortex has the duty of destroying poisons which come from without the body. That the cortex may exert antidotal properties is suggested by Myers' (526) observation that cobra poison, after being mixed with an emulsion of the adrenal cortex, was no longer toxic, control experiments with emulsions of the medulla and of

other organs giving negative results. Experimental infections with various organisms, such as the tubercle bacillus, and with toxins, such as the diphtheria toxin, give rise to hypertrophy of the cortex, and in some instances apparently to deficiency of the medulla.<sup>1</sup> Ritchie and Bruce (608) report in diphtheritic toxæmia in guinea-pigs exhaustion of all adrenin from the adrenal medulla.

Bogomolez (119) finds that in cats after experimental botulismus there is a hypersecretion of the lipoid substance of the cortex.

(3) It has often been suggested that in the cortical cells the material which is to furnish the active agent of the medullary secretion—the adrenin—passes through the initial stages of formation, and that the process of elaboration is completed in the medulla. This view has been tentatively proposed by Schäfer and Herring (628), and more definitely formulated by Abelous, Soulié, and Toujan (17, 23). These authors believe that the active principle can be obtained in small quantities from the cortex, where it is manufactured from tryptophane. It is then passed into the medulla and stored there. These views have not received support, and the experimental evidence in their favour is not convincing.

Elliott and Tuckett (239) have made an attempt to solve the problem of a possible functional relationship between cortex and medulla. Among mammals the guinea-pig is conspicuous by the huge development of its adrenal bodies, the growth being chiefly of cortex. They point out also that the lower the animal is in the scale of vertebrates the larger is its stock of chromaphil tissue. Gestation accelerates the growth of the gland.

As signs of secretory activity Elliott and Tuckett recognize four substances in the glands :

1. A fatty substance.
2. A doubly refracting substance.
3. Brown granules of the cortex.
4. The chromaphil substance of the medulla.

<sup>1</sup> Oppenheim and Loeper (541, 542, 543), Oppenheim (540), Bigart et Bernard (109, 110), Langlois (440, 443), Pettit (570).

Bardier and Bonne (69, 70) in studying the modifications produced in the structure of the adrenals by tetanization of muscles, found that these affected the cortex of the gland, not the medulla.

The first two are nearly related ; the doubly refracting substance increases with rest, when the fat becomes less abundant. In phases of " exhaustion " the doubly refracting substance vanishes and the fat spreads over all the cortex. But neither are essential factors in a generalized type of cortical activity, for neither appears in the sheep. The brown granules occur characteristically and plentifully in the guinea-pig, and over a restricted area in the ornithorhynchus. They accumulate with rest, and disappear very early in exhaustion ; the cytoplasm of the cells in which they have been stored then develops fat. Exhaustion of the medulla is shown by a progressive thinning of its yellow stain with potassium bichromate. In states of extreme exhaustion this stain finally vanishes.

The only indication found by Elliott and Tuckett of any functional relationship between cortex and medulla is the observation that the changes described above, both in cortex and medulla, move in close parallelism with one another in pathological states of the body. On the other hand, stimulation of the splanchnic nerves seems to affect chiefly the medulla (see p. 217 *et seq.*).

The enormous development of the adrenal cortex in the human embryo is possibly connected with the highly developed brain of man. Alexander has suggested, and Kohn supports the suggestion, that the connection may depend upon a lecithin product in the adrenal cortex in accordance with the lecithin requirements of the growing brain.

It must be confessed that both as to the function of the cortex and as to a possible relationship between it and the medulla, we are still quite in the dark.<sup>1</sup>

#### S. Summary of Views as to the Probable Functions of the Adrenal Bodies.

There have been two chief rival theories as to the function of the adrenal glands taken as a whole. These are the " antitoxic " and the " internal secretion " theory. Since

<sup>1</sup> Other papers on the general physiology of the two portions of the adrenal bodies are : Alezais (39), Hallion (347, 348), Guieysse (341), Reil (601).

Shattock and Seligmann (645) have recently called attention to the sensitivity of the subcutaneous tissues to adrenal grafts, which produce in them, œdema and hæmorrhagic solution (guinea-pig).



the discovery of the active principle of the medulla (adrenin), and the general recognition of the different origin, structure, and chemical nature of the cortex and medulla, the anti-toxic function has been chiefly assigned to the cortex, while the internal secretion has been supposed to belong to the medulla.

There is considerable evidence, both anatomical and physiological, to show that adrenin is the product of a secretory activity on the part of the chromaphil cells of the adrenal medulla, and that it passes by way of the adrenal veins into the general circulation, in order to assist the activity or maintain the tone of sympathetically innervated muscle and other tissue. It is interesting to note in this relation that the chromaphil cells of the medulla are derived from the cells of the embryonic sympathetic system. It is probable that the same function must be assigned to other parts of the chromaphil system.<sup>1</sup>

There are some reasons for suggesting that the cortex may yield a hormone (possibly of the nature of a complex lecithalbumin, derived from the lipoid granules of the cortical cells) which influences the growth and nutrition of certain tissues and organs, and especially the organs of reproduction. This theory may possibly find some support from the fact that the cortex is derived from the germinal epithelium. An antitoxic function has also been claimed for the cortex.

There is no evidence of sufficient weight to induce us to conclude that there is any functional connection between

<sup>1</sup> The question as to the internal secretion of the chromaphil tissues is one of extreme difficulty, when we bear in view the facts of comparative anatomy and histology. There are three possible views: (1) That all chromaphil cells, whether forming the medulla of the mammalian adrenal or paraganglia, or existing as scattered groups of cells in the sympathetic ganglia or nerves, form an internal secretion (for they all contain adrenin). (2) That only the chromaphil cells of the adrenal medulla have an internal secretion, while the cells in other places have not. This would involve the assumption that in the medulla of the adrenal the cells are glandular (arranged in the form of a gland), while in the other situations they are simply scattered groups and not glandular. This view might be taken to imply that these scattered groups are "vestigial remains" of the primitive paraganglia of Elasmobranchs, while the adrenal medulla is a fully developed gland. It is difficult to conceive that a few cells in the course of a sympathetic nerve manufacture an internal secretion. On the other hand, all these groups of cells contain adrenin; what, then, is its function or the significance of its presence? (3) That the chromaphil cells nowhere have the function of internal secretion. This is Kohn's view.

cortex and medulla. On the other hand, there are reasons derived from comparative anatomy, embryology, and pathology, for believing that the internal secretion of the cortex is independent of that of the medulla ; but we must not be too dogmatic on this point, for the ontogenetic and the philogenetic coming together of the two kinds of tissue may, after all, not be without some significance, which is at present unknown.

Several competent observers contend that although the powerful active principle—adrenin—is obtained only from the chromaphil tissues, yet the cortex of the gland is more essential to the life of the animal.<sup>1</sup>

<sup>1</sup> Elliott (*Proc. Physiol. Soc., Journ. of Physiol.*, 1912, xliii., p. xxxii) finds that the irritation of a cerebral puncture and hæmorrhage and simple ether anaesthesia are attended by a centrally excited loss of adrenalin through the splanchnics. His experiments were performed upon cats. I have not been able to obtain similar results in the case of the dog.

Glynn (*Quart. Journ. of Med.*, January, 1912, vol. v., No. 18, p. 157) has put forward considerable new evidence, derived from the study of adrenal tumours, that there is an intimate connection between sex characters and the adrenal cortex.

## CHAPTER XII

### THE CAROTID AND COCCYGEAL BODIES

#### A. The Carotid Body.

##### *Historical.*

THE carotid body has been known for a very long time. Neubauer (16) described and depicted the body in the year 1786, and Haller (5) had mentioned it many years previously.

Andersch (1) was the first to call the body the "gangliolum intercaroticum."

In the nineteenth century, Mayer (15) rediscovered the body and showed that it is an organ of constant occurrence.

It was Luschka (11) who substituted the name "glandula carotica" for Andersch's "gangliolum intercaroticum," and thereby initiated a controversy which has lasted up to the present time. He was struck with the difference between the "ganglion intercaroticum" and the other ganglia of the sympathetic. A careful examination convinced him that the structure was not a ganglion, but a gland made up of cell columns and vesicles. He could find only a few nerve cells in the body.

The glandular tubes and vesicles described by Luschka were regarded by Arnold (2) as ramifying branches of the artery which supplies the body, while the epithelial cells are those of the lining wall of the bloodvessels. This author proposed the name "glomeruli arteriosi intercarotici." Pförtner (17) supported the view of Arnold, while Heppner (7) was in favour of the theory put forward by his teacher, Luschka.

Eberth (4) places the carotid body side by side with the coccygeal ("plexus vasculosus coccygeus") as the "plexus arteriosus caroticus," and this view was adopted by anat-

mists generally. Henle (6) adopted Andersch's name, while partially agreeing with Eberth's description.

Stieda (22) adopts the name employed by Luschka, and declares himself an adherent to his views. In addition, he states that the gland is developed from the epithelium of a branchial cleft.

Katschenko (9) investigated the development of the carotid body in the pig, and reported that it is not of epithelial origin. It is formed in the outer coat of the carotid artery, and is intimately related to the neighbouring nervous ganglia.

Marchand (13) describes the development of the carotid body in the human subject, and, as to the general nature of the organ, held opinions very similar to those of Arnold. He suggests the name "nodulus caroticus," and considers the body in question to be a rudimentary organ.

Stilling (23) made the important discovery that the carotid body contains some cells which stain brown with potassium bichromate. This observation was confirmed by Kohn (10), who has added to the long list of names attached to this tiny body, by suggesting that it be called the "paraganglion intercaroticum."

#### *Comparative Anatomy and Embryology.*

In the human subject the carotid glands are small bodies situated just above the bifurcation of the common carotid artery on each side, and between its internal and external branches. According to Luschka (11), the gland is of an elongated spherical shape, 5 to 7 millimetres long, 4 to 2½ millimetres broad, and 1½ millimetres thick. Sometimes it is divided into two or more nodules. The body is greyish or brownish-red in colour. Its consistence is more compact than that of a nerve ganglion, and its substance cannot be easily teased out with needles.

In all, or in nearly all mammals so far investigated, the carotid body has been found in the neighbourhood of the bifurcation of the common carotid artery, either exactly at the bifurcation or somewhat higher up in the connective tissue between the internal and external carotid arteries. Both these and the common carotid may give twigs to the body.

Many observers have noted the richness of the nerve-supply to the carotid body ; this supply is mostly from the sympathetic nervous system. According to Luschka, there is situated between the internal and the external carotid arteries a rich nervous plexus beset with tiny ganglia—plexus intercaroticus—which is a complex of fibres from the superior laryngeal and the glosso-pharyngeal nerves, and a variable number of twigs from the superior cervical ganglion. According to Svitzer (25), there are twigs to the body from the superior cervical ganglion, from the nervi molles Halleri, from the trunk and the pharyngeal branch of the vagus, from the superior laryngeal branch of the vagus, from the hypoglossal, and from the sympathetic above and below the superior cervical ganglion.

According to Maurer (14), the body is absent in fishes, but present in Amphibians and all higher vertebrates. In the Anura an epithelial bud occurs in the region of the second gill-cleft, which at first resembles the parathyroids from clefts 3 and 4, but soon becomes distinguished by its relation to the branchial arteries. Zimmerman (28) states that there are no epithelial elements, but only a proliferation of the vascular wall. Maurer believes that the carotid body of *Rana* is homologous with the carotid body of higher vertebrates. The matter is doubtful in reptiles and birds, though Maurer believes that in *Echidna* the origin of the structure is the same as in the frog. Schaper (19), however, believes that in mammals the body is a development of the wall of the artery. Maurer acknowledged that our knowledge of the development is still very imperfect, and suggests that under a single name several different structures have been described. Kohn (10) believes that the carotid body is derived from the embryonic ganglion cells of the sympathetic plexus.

#### *Microscopical Structure.*

According to Kohn, there are four principal types of the organ according to the arrangement of the cellular elements. In the first type the body is compact and circumscribed. The connective tissue is so finely divided that the cellular character of the tissue is predominant. The carotid gland of the cat is a good example of this type. (See Fig. 48.)

In other cases the connective tissue is distributed into the gland in larger amount, and so two new types arise. In one of these the organ has a kidney-like form. At the hilus there is a considerable accumulation of connective tissue with bloodvessels and nerves. From this region radial septa run into the interior, which divide up the organ into lobules after the manner of a secreting gland. The lobular formation is found typically in the carotid gland of the monkey (*Macacus rhesus*).

In man the gland is divided by its connective tissue into small separate islets.

The fourth type is exemplified in the carotid body of the rabbit, which consists of scattered islets and strands of cellular tissue. This may be called the diffuse type (Kohn).

The cells are of variable, for the most part of considerable, size. Their form is manifold; they may be prismatic or cylindrical, but they are frequently flat. Kohn does not deny that there is a certain resemblance to an epithelial structure,



though he is opposed to the view that the chromaphil tissues are of a secretory nature.

The cell body is finely and uniformly granular. The nucleus is large, granular, and shows a distinct nuclear membrane and nucleoli. As a rule there is one nucleus, but there may be two. In some cells the nucleus is so poor in chromatin that the cell resembles a nerve cell. Many cells, moreover, possess a cell membrane.

Kohn (*loc. cit.*) gives other details. The essential point, however, is this, that all the true specific cells of the body are chromaphil cells—that is to say, they become stained of a yellowish or brownish tinge by solutions containing bichromate of potassium. Kohn states that the degree of coloration varies within very wide limits. The cells are arranged in groups, and the body is permeated

FIG. 48.—Portion of a section through the carotid body of a cat. (Drawn by Mrs. Thompson.)

by non-medullated nerve fibres and scattered nerve cells.

The organ is richly provided with bloodvessels. The arteries break up into a close capillary network, which penetrates the cell groups, and where the amount of connective tissue is small, come into close contact with the cells.

Kohn lays great stress upon the intimate relation existing between the nerve fibres in the body and the specific carotid cells.

The carotid body is developed from the embryonic ganglion cells of the intercarotid sympathetic plexus.

From the foregoing account it would seem that we are justified in including the carotid body in the category of the chromaphil tissues. The body, then, has no special functions, other than those of the chromaphil tissues generally, and all that has been said on the pharmacodynamical effects of adrenin, the chemistry of adrenin, and the functions of the adrenal medulla, applies in all probability to the carotid body.

### B. The Coccygeal Body.

The coccygeal body in the human subject is a small organ, at most 2.5 millimetres in diameter, sometimes broken up into a number of smaller bodies, placed immediately in front of the apex of the coccyx, and receiving branches of the middle sacral artery [Schäfer and Symington (18)].

The body was discovered by Luschka (12) in 1860, and since that date various opinions have been held in regard to its structural elements and its essential nature. These opinions have been classified by Schumacher (20) as follows :

1. The cells of the body are not constituents of the vessel walls, but thread-like accumulations of specific cells, into which bloodvessels penetrate [Luschka, Sertoli (21), Walker (27)].

2. The cells are constituents of the bloodvessel walls :

- (a) They are derived from the endothelium [Arnold (3)].

- (b) They are derived from the adventitia ("perithelium" cells) [Waldeyer (26), v. Hleb-Kosznanska (8)].

(c) The cells are related to those of the middle coat of the middle sacral artery and its branches [Stoerk (24)].

Schumacher (20) has given a full description of the "glomus coccygeum" in the human subject, and the "glomeruli caudales" of other mammals. According to this author, the former corresponds in all essential points to the latter, the only difference being that the "glomeruli caudales" of animals consist of several detached portions corresponding to the caudal segments, while the "glomus" of man is represented by a principal structure at the tip of the coccyx and some smaller nodules.

It has been shown by Stoerk (24) that the cells of the carotid body do not give the chromic reaction at any period of life, and that they bear no histogenetic relation to the sympathetic nervous system.

The "glomeruli caudales" and the "glomus coccygeum" appear to be arterio-venous anastomoses (Schumacher), and the epithelioid cells are transformations of the smooth muscle fibres of the middle coat of the artery.

The structures in question are probably to be regarded as safety-valves in the course of the peripheral circulation. The balance of evidence is against their having any kind of internal secretion.



## CHAPTER XIII

### THE FUNCTIONS OF THE THYROID AND PARATHYROIDS

#### **A. Introductory : The Organs derived from the Region of the Pharynx and Gill-Clefts.**

THE organs in question may be divided into two groups. The first group is represented by structures which arise simultaneously with the gills and gill-clefts—viz., the thyroid, the thymus, and the post-branchial bodies (the suprapericardial bodies of v. Bemmelen). The organs of the second group are developed concomitantly with the degeneration of the gills and the closing of the clefts, from whose epithelium they arise. These are the “branchial bodies” of the Anura and the parathyroids throughout Amniota.

Our knowledge of the first group we owe in the first instance to the works of Remak (483), Kölliker (306), W. Müller (415, 416), His (244, 245, 246, 247), Dohrn (120), and v. Bemmelen (30, 31, 32, 33, 34). The development of the organs of the second group was first made clear in the Amphibians by Maurer (372, 373).

#### **B. The Comparative Anatomy and Histology of the Thyroid and Parathyroid Bodies.**

1. In *Amphioxus* and *Ammocœtes* the thyroid is a sausage-shaped glandular body which branches in a fork-like manner and retains its opening into the pharynx [Maurer (376)]. This indicates a relationship to the hypobranchial furrow of *Tunicates* [W. Müller (415, 416)]. The epithelium lining this saccular gland is ciliated, and secretes mucus.

In *Petromyzon* the connection with the pharynx is broken, and the gland consists of a number of closed vesicles lined by tall columnar epithelium, and containing a colloid substance in their interior [Schneider (530)].

2. Simon (552) found the thyroid in all classes of **Fishes**, and the work of Robin (491, 492, 493, 494), Legendre (327), and Guiart (207) contributed largely to our knowledge of this organ in Elasmobranchs. In this group the thyroid is a moderately large compact organ situated at the anterior end of the ventral aorta, in front of the bifurcation of the branchial artery. The gland is yellowish-white in colour, and the anterior extremity is elongated and prolonged to a point in some species. In other species the thyroid is nearer the end of the tongue, situated on the coraco-hyoid muscles, immediately under the coraco-mandibular, and may be spheroidal, flat, or irregular in shape. Groups of follicles are sometimes detached, forming accessory thyroids [Guiart (207)].

The histology of the thyroid gland in the cartilaginous fishes, as well as in vertebrates generally, has recently been investigated in the laboratory of the present writer, by Mrs. F. D. Thompson (576). There is a striking uniformity in the general microscopic appearance of the thyroid gland throughout all vertebrates above the Cyclostomata, and the thyroid of the Elasmobranch fishes would be immediately recognized as such by any student who had once seen under the microscope a preparation made from the mammalian thyroid. Such differences as are found throughout vertebrates, in regard to the amount of intervesicular connective tissue, intervesicular epithelial tissue, size of the vesicles, and so on, are equally to be recognized among the glands of Elasmobranchs themselves.

Perhaps the most interesting of the species examined is *Scyllium canicula*. In this fish the thyroid contains not only the usual vesicles, but also several bodies composed of two kinds of cell—lymphoid and epithelial. Since parathyroids have not been described by the embryologist, these bodies are probably nodules of thymus.

Throughout Elasmobranchs the shape of the cells lining the vesicles varies extremely in different species. Thus, in some it is of a tall columnar, and in others of a low cubical form. The colloid contents appear to be of the same character as in other vertebrates.<sup>1</sup>

<sup>1</sup> Goodey (200) finds remains of a thyroid duct in *Chlamydoselachus anguineus*, as well as in *Scyllium canicula*.

3. In Teleostean fishes the thyroid was described by Stannius (560), in 1854, and in 1884 McKenzie (386) gave an account of the anatomy of the thyroid in *Amiurus*. According to this writer, the gland is placed beneath the copulæ of the branchial arches and surrounds the anterior end of the branchial artery. It is an unpaired structure extending in the median line from the origin of the vessels at the first pair of gill arches to a short distance behind the origin of the single stem for the third and fourth pair of arches. Although richly supplied with blood, it appears of a whitish colour contrasted with the bloodvessels among which it lies. The framework of the organ consists of loose connective tissue which does not form a lining membrane, but simply passes over into the like tissue sheathing the adjacent parts and the vessel which it surrounds. The usual vesicles of the thyroid are scattered throughout this connective tissue, showing a tendency to arrange themselves in short rows. They vary in size from  $15 \mu$  to  $210 \mu$  in diameter, and are filled with the usual colloid substance. A few, however, contain a granular substance with nuclei showing nucleoli scattered through it, while others are partly filled with the granular and partly with the colloid matter. The wall of the vesicle consists of a single layer of columnar epithelium resting on a basement membrane formed from the surrounding connective tissue. The epithelium is readily made out in the young fish, but disappears frequently in the adult.

In the conger Legendre (327) describes two posterior lobules contiguous to the trunk of the branchial artery, and following its course while gradually diminishing in volume. In the carp and the tench the two lobules have about the volume of a pea.

According to Maurer (371), the thyroid of Teleosts consists of a mass of follicles (more or less separated from one another) which surrounds the trunk of the branchial artery from the heart to its extremity.

Guiart (207) gives some description of the thyroid in Teleosts, as also does Mrs. Thompson (576), who finds that in *Amiurus* the connective tissue in which the vesicles lie is very compact and not loose, as described by McKenzie. Further, in none of the slides was the epithelium columnar, and the statement that the cells of the vesicles rest upon

a basement membrane could not be verified. In an embryo specimen the vesicles were filled not with colloid, but with some material full of nuclei [epithelium or adenoid tissue (?)].

The thyroid of Teleostean fishes is of special interest owing to the fact that goitre (active thyroid hyperplasia) is not uncommon [Marine and Lenhart (362, 363), Guder-natsch (206)], which is stated to become carcinomatous. The tendency of the growth to spread seems to be connected with the fact that the gland is not circumscribed, has no capsule, and so the gland follicles are distributed over a wide area, and outstanding groups of cells may become fresh foci of tumour formation.

No parathyroids have been found in fishes, but the post-branchial body is developed.

4. In the *Urodela* the thyroid occupies a more superficial position than in the *Anura*. The development has been worked out in *Triton*, *Siredon*, and *Necturus*. The gland arises from a median rudiment, and subsequently becomes paired.

In *Sperlerpes ruber* the vesicles are approximately of the same size as in the frog. According to Mrs. Thompson (576), they do not number more than a dozen. There is less connective tissue than in the frog, and the vesicles are therefore more closely packed together. The colloid contents are of the same character as in vertebrates generally. The gland is distinctly more vascular than in the frog.

In *Triton* there appear to be two, or even three, parathyroids developed on either side. In *Sperlerpes* there is sometimes only one. The general histological features appear somewhat different from those of the corresponding structure in the frog. The body is of extremely small dimensions, but contains fairly large blood capillaries. It is encapsuled, but its constituent cells do not possess the whorl arrangement so characteristic of the parathyroids of the frog.

The post-branchial body occupies a corresponding position to that in the frog; it consists of about eight vesicles. These have a taller epithelium than the thyroid vesicles and contain colloid [F. D. Thompson (576)].

5. In the *Anura* (*a*) the thyroid has been most carefully studied in the frog. In this animal the gland of each side

is an oval corpuscle placed ventrally to the root of the processus postero-medialis of the hyoid cartilage, and occupies a deep concealed position. It is very difficult, as a rule, to find by ordinary dissection.<sup>1</sup>

Like the thyroid of all animals, that of the frog consists of a number of closed vesicles, the walls of which are composed of a single layer of epithelial cells. The cells lining the vesicles are cubical, but small, corresponding with the small size of the vesicle and of the whole gland. The intervesicular tissue, instead of being cellular as in mammals, is formed of fibrous connective tissue with scattered nuclei and bloodvessels. The colloid contents of the vesicles call for no special notice.

(b) Accessory thyroids are not uncommon in the frog; they have the same structure as the main thyroid.

(c) Parathyroids in the frog are first mentioned by Ecker (127), who considered them as representatives of the thymus, and by Leydig (336), who considered them, together with the "ventral branchial body," as representing the thyroid. That they are very different from the thyroid in their structure Leydig himself stated. The suggestion that one of the bodies described by Leydig was the ventral branchial body and the other the parathyroid is made by Gaupp (177), and on referring to Leydig's monograph and looking at his plates, it seems clear that this is the case. After the work of Toldt (581), the bodies were called for some years "Nebenschilddrüsen," a term which has naturally led to much confusion, owing to the fact that the same term has been sometimes applied to the true accessory thyroids. The matter was finally made clear by Maurer (374), who recognized the homology of these organs with the glandulæ parathyroides which were discovered in higher animals by Sandström in 1880 (514), and independently by Baber (14), Horsley (260), and Gley (185).

The parathyroids of the frog are represented on either side of the body by two oval or spheroidal corpuscles placed one behind the other at the side of the jugular vein in the sinus sternalis. They are sometimes quite close to the ventral branchial body, and sometimes at some distance from it; they are greyish-red or yellowish in colour, and in

<sup>1</sup> For a detailed account of the anatomy of the frog's thyroid see Gaupp (177).

adult specimens of *Rana esculenta* may reach 1 millimetre in diameter [Gaupp (177)].

The arteries to the corpuscles come from the musculoglandular branch of the external carotid. The veins pass into the external jugular.

There may be more than two glandules on either side.

The parathyroid has a tough, fibrous capsule, and the interior of the body is compact. There are closely placed elliptical or spindle-shaped nuclei which stain deeply. The cells are longish, and so disposed that they describe spiral turns. The cell outlines of the glandules are distinct even when viewed under a low power of the microscope. Some of the nuclei are rounded, while others are distinctly elongated. Some of the cells are vacuolated, probably owing to the removal of fat droplets in the process of preparation for microscopical examination. In some sections the disposition of the more central part of the organ is such as would be found if the body had been subjected to a process of torsion. The cells vary very considerably in shape; they may be oval, cubical, pentagonal, spheroidal, or elongated.

(d) The post-branchial body is of considerable importance in any discussion of the development of the thyroid body. Its relationship to the latter body in higher vertebrates will be fully discussed later (p. 269). De Meuron (392) was the first to discover the structure in the frog and in the toad, and to work out its development. He considered that it is homologous with the suprapericardial body which had been described by v. Bemmelen (31, 34) in Elasmobranchs. Maurer has supported this view, and introduced the name "post-branchial body" to express its relation to the gill-clefts. V. Bemmelen (31) looked upon his suprapericardial bodies as homologous with gill-clefts, but Maurer considers them to be of a different nature, because in all vertebrate animals in which they occur they arise immediately behind the last gill-cleft, whether this be the fourth, fifth, or sixth.

The post-branchial body has so far been discovered in all Craniata except the Cyclostomes and Teleosts, but in many forms it appears only on one side.

The body of the frog is a tiny structure which lies at the side of the aditus laryngis under the epithelium of the floor

of the pharynx. It consists of three or four small vesicles lined with cylindrical epithelium. Maurer states that these cells sometimes carry cilia. The vesicles contain a coagulated albuminous substance and débris, but no colloid.

6. In **Reptiles** the thyroid is unpaired in some families (Ophidia and Chelonia), while in the Lacertilia the organ is bilobed in young specimens, paired in older ones. The organ lies immediately in front of the pericardium. The parathyroids and post-branchial bodies are intimately united, paired, and placed anteriorly to the thyroid. Their precise anatomy differs in different groups. The thyroid gland presents no special features so far as microscopical structure is concerned.

In *Chrysemys picta* and *Pseudemys scripta* the parathyroid contains vesicles, and in the latter species some of these vesicles contain colloid.

In *C. picta* the post-branchial body also contains colloid [F. D. Thompson (426)], but the parathyroid and post-branchial body are very considerably confused together in this and some other species.

In *Testudo græca* there exists on each side an "inferior internal" parathyroid, applied to the carotid ("glandule parathyroïdienne"), and a "superior external" parathyroid included within the substance of the thymus ("glandule parathymique"). These bodies are about 1 millimetre in size, round, oval, or triangular, and possess processes which may be as long as the organ itself. The glandule which is embedded in the thymus is particularly rich in such processes (Aimé).

7. In **Birds** the general features of the thyroid are the same as in reptiles. The adult gland is a paired organ placed near to the large vessels of the neck. The vesicles are frequently small and irregular in outline. The intervesicular tissue is large in amount, and in certain regions and in certain specimens forms large areas of solid tissue, which is indistinguishable from parathyroid. This condition of affairs in the avian thyroid has been emphasized by Forsyth (163, 164, 165), and it has been pointed out (576) that from the very wide variations in the amount of the intervesicular tissue found in different specimens of the same species, and from feeding experiments, we must conclude that the pro-

portion between vesicular and intervesicular tissue varies under different physiological conditions.

The *parathyroid* of birds (see Fig. 49) contains an abundance of fat. It does not contain vesicles like those of the reptilian glandule.

In close relationship, and in some regions anatomically continuous, with the tissue of the parathyroid, we find a body having an extraordinary structure. It is obviously of epithelial nature, and is composed largely of structures which at first sight resemble small arteries, but whose walls

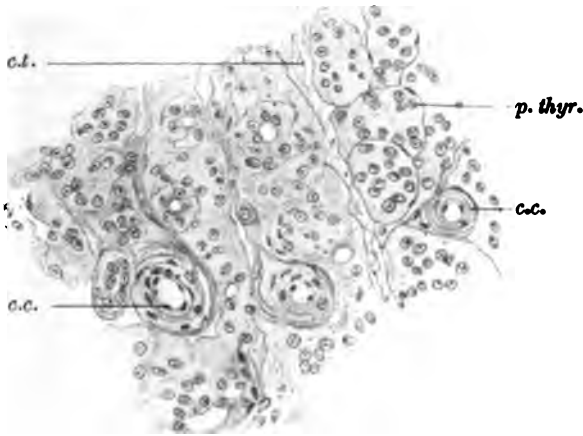


FIG. 49.—Pigeon. Portions of post-branchial body (on the left) and parathyroid (on the right), separated by a connective-tissue septum. Note the presence in both of structures identical with Hassall's corpuscles of the thymus. These are numerous in the post-branchial body, and few in the parathyroid. In both, the concentric bodies frequently show a lumen. (F. D. Thompson.)

c.c., concentric corpuscles ; c.t., connective tissue ; p. thy., parathyroid.

are composed entirely of concentrically disposed spindle-shaped cells, and projecting into the lumen are irregular cells lining the tubules (Fig. 49). The rest of the body appears to be made up of structures identical with the various well-known forms of Hassall's concentric corpuscles of the thymus. There is a mass of this tissue in the centre of the parathyroid, and small portions of it in other regions of the glandule. There are also true thymus nodules in close connections with the body. Thus the structure which is commonly called the *post-branchial* body in birds (a



yellowish-white body some little distance posterior to the thyroid), is composed not only of post-branchial tissue, but also of parathyroid and thymus [F. D. Thompson (576)].

While the birds illustrate fairly well what will be fully insisted upon later in regard to other groups of animals—viz., an intimate relationship and anatomical continuity between thyroid, post-branchial body, and parathyroid, it must be admitted that, as regards the essential relationship between thyroid and parathyroid, the evidence is not so convincing as in mammals. Although a parathyroid is derived from both third and fourth clefts, yet the one derived from the latter does not become enclosed in the thyroid tissue as is the case in mammals.

Forsyth (163, 164, 165) has largely employed birds to support the thesis, urged by the present writer and his co-workers, as to the intimate relationship subsisting between thyroid and parathyroid. Although recent investigations fully support these conclusions so far as they relate to mammals, it would seem that the intimate physiological and anatomical connections obtaining in mammals have not yet come fully into existence in birds.

8. **Mammals.**—(a) The general position and anatomical relations of the thyroid in mammals is too well known to call for a description. It will, however, be useful to describe in a series of mammals the probable number and the usual position of the parathyroids in relation to the thyroid.

The parathyroids of mammals are usually four in number. They are small, oval, or spherical bodies, in most cases of a distinctly lighter tint than the thyroid tissue, and occupy very variable positions not only in different species, but in different individuals. On either side of the median line of the body there are typically two of these glandules, which are referred to at the present time either as "external" and "internal," or as "parathyroid III." and "parathyroid IV." respectively, the Roman numeral indicating the number of the gill-cleft from whose epithelium the gland was originally formed. The latter mode of signification is by far the most precise, but the majority of writers prefer to refer to an external and an internal glandule on either side. The terms "external" and "internal" appear, however, to be used by different authors in different senses. Kohn's

definition of the terms is given in the following words: "Das eine lag in der Regel der Aussenfläche der Seitenlappen lose an, das andere innerhalb derselben. Ersteres wurde 'ausseres,' letzteres 'inneres' . . . genannt" (230). By "external" and "internal" here is implied "on the surface of" and "in the interior of" respectively. But Schäfer (523) interprets the terms differently. Thus, "there is one parathyroid" ("outer epithelial body") constantly to be met with in mammals on the lateral surface of each lobe of the thyroid, and another on the mesial surface of each

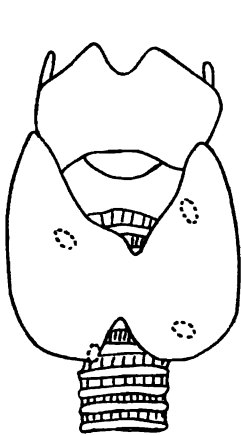


FIG. 49a.—Semi-diagrammatic sketch showing the position of the parathyroids, the thyroid, and the trachea in the human subject. Front view. Parathyroids projected on to the surface.

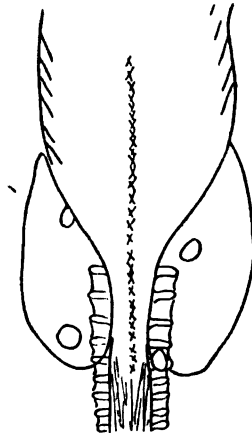


FIG. 49b.—Semi-diagrammatic sketch showing the position of the parathyroids in the human subject. Posterior view.

lateral lobe ("inner epithelial body"). So also Forsyth (165).

Despite this confusion in terminology, for most animals, at any rate, the terms "external" and "internal" are sufficiently suitable for designating the two parathyroids respectively ("III." and "IV."), because it so happens that the glandule which lies on the surface of the gland lies also in the majority of cases on the lateral aspect of the lobe, and the one which is buried in the thyroid substance is nearer the mesial surface.

(b) In *Man* the anatomy of the human thyroid is too

well known to need any description. It belongs to the group of thyroids possessing an isthmus. There are many points of interest, embryological and surgical, connected with some common varieties, but there will not be space to treat of these.

The *parathyroids*, according to most observers, are four in number—two on each side of the median line of the body. The average dimensions are about 6 or 7 millimetres in length, 3 or 4 millimetres in breadth, and 1·5 or 2 millimetres in thickness. The length is very variable, while the thickness is fairly constant. In shape they are oval or pyriform, and they may be connected by a stalk, in which run the parathyroid vessels, to the thyroid gland. The average weight is 0·035 gramme. There seems to be no relation between the weight of the parathyroids and that of the thyroids. The parathyroids are of a lighter colour than the thyroids, and yellowish owing to the presence of fat. The surface is smooth and soft.

The two glands on each side are described under the names of the “posterior superior parathyroid,” and an “anterior inferior” parathyroid, the names indicating their relation to each other. (See Figs. 49a and 49b.) The posterior superior glandule is more constant in position than the anterior inferior. It lies usually on the posterior wall of the œsophagus or pharynx at the level of the lower edge of the cricoid cartilage, immediately internal to the posterior margin of the lateral thyroid lobe, and in front of the prevertebral division of the cervical fascia. The parathyroid is usually separated from the thyroid by a septum of connective tissue.

The anterior inferior thyroids are very inconstant in position and relations. Sometimes their position is more anterior, sometimes more posterior, and they may, especially in the former case, be placed very low down, even at the level of the tenth tracheal ring [Welsh (632), Fusari (175), Chantemesse and Marie (79), Forsyth (165), Halsted and Evans (223).<sup>1</sup>

(c) *Monkey*.—The writer is not acquainted with any description of the parathyroids in the anthropoid apes. In the different species of monkey usually employed for opera-

<sup>1</sup> This paper gives an excellent account of the blood-supply to the glandules.

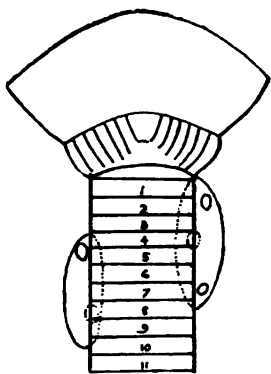


FIG. 50.

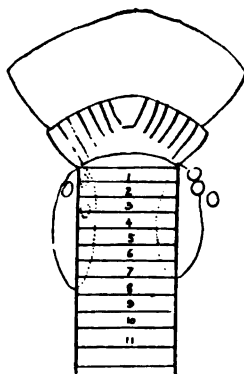


FIG. 51.

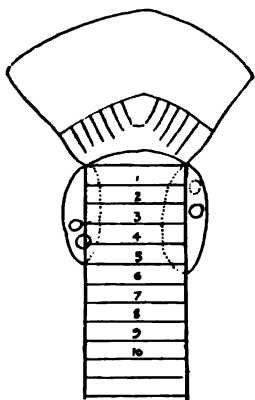


FIG. 52.

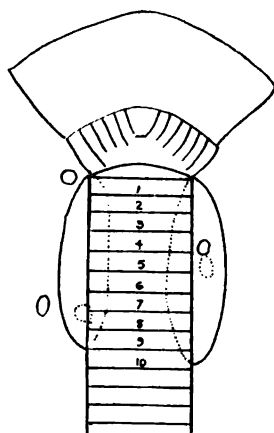


FIG. 53.

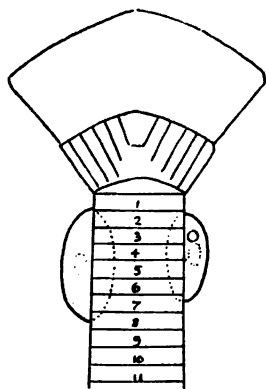


FIG. 54.

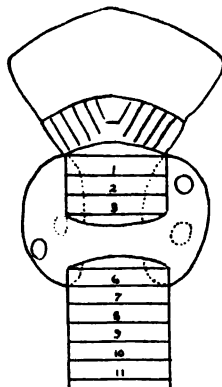


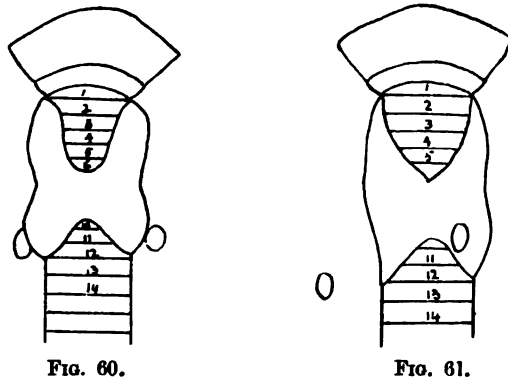
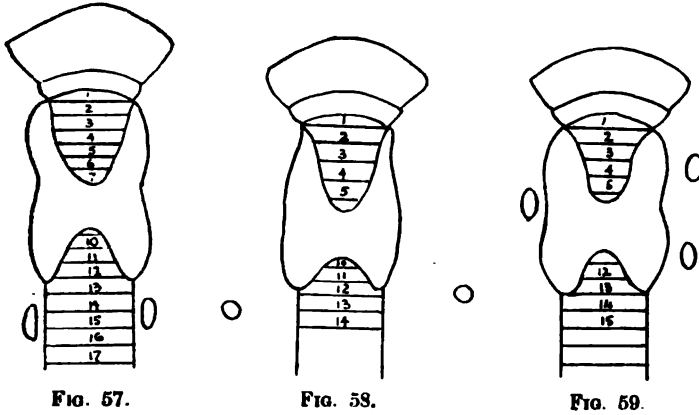
FIG. 55.

FIGS. 50 to 55.—Semi-diagrammatic sketches showing the position of the parathyroids, the thyroid, and the trachea in the dog. The parathyroids in dotted lines are "internal."



is very rarely found that the internal parathyroids can be seen on both sides (615). (See Figs. 50-55.)

(e) *Cat*.—In the cat, as is most usual throughout mammals, there are four parathyroids, two internal and two external. Their arrangement resembles that in the dog. (Fig. 56.)



Figs. 57 to 61 are semi-diagrammatic, and show the relationship of the thyroid, external parathyroids, and trachea in a series of rabbits. The "internal" parathyroid is not shown, since it was found only on microscopical examination.

(f) *Rabbit*.—There are usually four parathyroids, but the external glandules are uniformly placed at a considerable distance from the thyroid lobe. For this reason, in the earlier extirpation experiments they were always left behind at the time of the operation. (See Figs. 57-61.)

(g) In the *Guinea-pig* the distinction between internal and external parathyroids seems largely to break down. There are usually four parathyroids, sometimes three, or even only two. (Figs. 62-66.)

(h) In the *Rat* the thyroid consists of two lobes united by

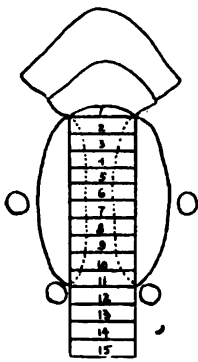


FIG. 62.

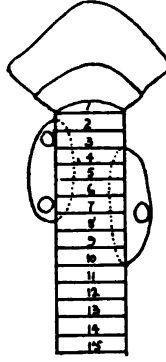


FIG. 63.

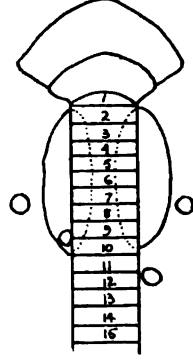


FIG. 64.

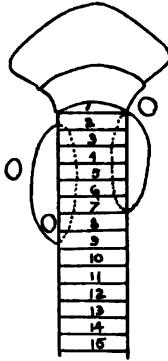


FIG. 65.

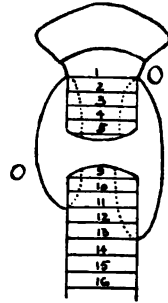


FIG. 66.

FIGS. 62 TO 66.—Parathyroids in the guinea-pig. The extreme variability in number and position is shown. In none of this series were any true "internal" parathyroids seen with the unaided eye.

an isthmus. There is only one parathyroid in connection with each thyroid lobe, and this seems to correspond with the external body of the cat and dog [Vincent and Jolly (615), Thompson (576)].

(i) In the *Wolf* and *Badger* there are four parathyroids whose precise location does not call for any description.

The general arrangement conforms fairly closely with that in the dog and cat.

(j) In the *Pig* the internal parathyroid is stated to be absent [Ellenberger (144)]. In this animal and in *Ruminants* the external parathyroid is not close to the thyroid, but is in connection with the thymus. In the ox, in addition to the four typical parathyroids, it is stated that there are accessory parathyroids of macroscopic size in different regions of the neck and mediastinum [Rossi (507)].

(k) In the *Horse* the relationships of the parathyroids have not been fully ascertained. In a recent paper Estes (119) states that the external glandule of the horse is found in close relation to the upper end of the thyroid or in the perithyroid areolar tissue. The internal parathyroid is variously placed beneath the capsule of the thyroid, usually near its upper pole. The external gland is much the larger. The horse then appears to resemble the other Herbivora in the distribution of its parathyroids.

(l) In *Sheep* and *Goats* there are two parathyroids embedded more or less in the thymus, and two others in the substance of the thyroid [MacCallum, Thomson, and Murphy (262)].

### C. Histology of the Thyroid in Man and Mammals.

The larger lobes of the thyroid are surrounded by a thin capsule of connective tissue, and are divided, by processes running into the interior of the organ, into smaller and smaller lobules. The ultimate lobules are of irregular form and size, but are, for the most part, roughly circular or oval in section, and have a diameter of about 0.5 to 1.0 millimetres. The interior is mostly occupied by vesicles of varying size, 45  $\mu$  to 110  $\mu$  [v. Ebner (126), Kölliker (307)], 80  $\mu$  to 220  $\mu$  [Ch. Simon (552)], and varying shape. It was formerly thought that the gland was made up of a system of branching alveolated canals [Virchow (620), Boéchat (53), Zeiss (650), Hitzig (248)]; but it has been conclusively shown by Streiff (564) that the glandular substance is composed of closed vesicles, which are separated from one another by fine strands of connective tissue, and a variable amount of an intervesicular cellular tissue. Most of these vesicles are of roundish, long, oval, or polyhedral form, but



occasionally one meets with forms somewhat resembling the tubules of alveolar glands, only that they are closed at both ends; these have sometimes side branches, or two or three large vesicles may freely communicate with each other. In many lobules one finds in addition to the vesicles solid cords and nests of epithelium cells. These are more numerous in the young and developing thyroid.

The ensheathing capsule of the organ and the interlobular connective tissue consist of bundles of white fibres with numerous elastic fibres. This connective tissue carries numerous bloodvessels and lymph vessels into the interior of the lobules, and finally surrounds the vesicles of the gland substance. The vascular connective tissue comes into immediate contact with the epithelial lining of the vesicles. According to Langendorff (318), Schmid (529), Zeiss (650), and Baber (14), there is no *membrana propria*; the vesicle is enclosed by very fine bundles of connective-tissue fibres, outside of which is the endothelium of the lymph spaces.

The epithelium cells lining the vesicles are of a fairly uniform, cubical, or columnar form,  $9\ \mu$  to  $13\ \mu$  in height. According to Schmid (529), they tend to become flatter in old age, but cylindrical cells are not uncommonly found, even in the adult. When examined in 0.75 per cent. normal saline, the epithelial cells of the human thyroid show, in most instances, a number of granules of varying size. These are chiefly aggregated in the part of the cell next to the cavity of the vesicle; they are highly refractive, and show a characteristic greenish tinge. These are apparently of a fatty nature; but, in addition to these, there are found in the cells smaller granules of a different character. The larger granules appear to be characteristic of human thyroid.

According to Langendorff, the epithelium cells are of two kinds—"Hauptzellen" and "Colloidzellen." In osmic-acid preparations stained with the Ehrlich-Biondi mixture, the former are unstained, while the latter appear red with green nuclei. According to v. Ebner (126), these do not represent two distinct varieties of element, and there is nothing in the vesicular epithelium corresponding to the two kinds of cell in the glands of the stomach. The cell protoplasm shows a retiform structure, with frequent longi-

tudinal striation. The nuclei are spherical, have a homogeneous appearance, or show a very fine chromatin network. As in other gland epithelia, mitosis is only to be observed in young individuals [Schmid (529)]. Zimmermann (651) describes a double centrosome close to the free surface of the cell.

Occasionally one finds solitary cells in the interior of a vesicle. These are normal epithelium cells, which have become separated from the lining layer of the vesicle. Sometimes they are in a good state of preservation; mostly, however, they appear to be in some state of resorption. The nucleus stains faintly. According to v. Ebner (126), leucocytes do not occur either in the epithelium or in the cavity of the normal vesicle.

As regards the contents of the vesicles, they are filled with the yellowish sticky fluid which is observed to flow from the cut surface when the gland is cut. The earliest writers upon the subject thought that the whole vesicle was filled up with cells [Schwager-Bardeleben (540)]; but, in 1847, Panagiotades (447) gave a description which corresponds in outline with the modern conception. In the second edition of the "Gewebelehre," in 1855, Kölliker (305) describes the vesicular contents as a yellowish liquid containing much protein. The abundant presence of cells and their débris in the interior of the vesicle he considers due to post-mortem changes. Verson (606) states that the free surface of the cell wall may be seen to project irregularly, and spheroidal, tenacious, and hyaline drops, which after some time coalesce in the centre of the vesicle, gradually develop from the bodies of the cells.

Peremeschko (459) found that the contents of the vesicles change with the age of the animal. In young embryos there is a finely granular mass, enclosing cells and nuclei. In larger embryos one finds occasionally vesicles filled with transparent masses of colloid; in young animals this is the case with the larger number of the vesicles, and in adults one rarely finds vesicles without colloid. In adult animals the colloid substance completely fills the cavity of the vesicles.

Virchow (620) describes lymphoid cells in the interior of the vesicle, which secrete an albuminous fluid, which later,

under the influence of the salts of the tissue fluid, becomes converted into colloid.

Zeiss (650) looks upon the colloid as nothing more than a concentrated form of the fluid originally appearing in the vesicles. In this fluid he often finds a lump of colloidal material, around the periphery of which new layers of colloid are being continually laid down, until the entire cavity is filled with a compact mass of colloid. The drops of secretion described by Peremeschko, Zeiss considers to be simply appearances due to shrinkage. He was never able to isolate the clear, transparent, unstainable drops.

Baber (14) finds in the vesicles, in addition to a small quantity of a clear substance, a solid mass which has retracted from the wall of the vesicle. By staining with picrocarmine it shows a finely granular structure, and is strongly differentiated by its yellow colour from the red-stained epithelial wall. Hæmatoxylin gives it an opaque grey or greyish-violet tinge, and shows a homogeneous or granular structure. The vesicle varies from time to time both as to the amount of the contents and as to their staining reactions, depending upon the state of functional activity of the gland.

According to Biondi (40), the vesicles contain a homogeneous substance which becomes dark and granular after fixation with osmic acid. This substance is a product of the epithelial cells, as shown by the fact that these frequently contain granules which have the same staining reaction as the colloid.

Langendorff (318) was the first to give a clear account of the micro-chemical reactions of the colloid substance. There is no doubt that the contents of the gland vesicles completely fill their interior. If these contents become hard as the result of chemical treatment, they may either preserve their original volume or may undergo change in this respect; if the hardening is the result of dehydration or heat, considerable shrinkage occurs. The best fixing agents are those which coagulate proteins without change of form, such as osmic-acid mixtures. If such be employed, one sees that the masses of colloid lie in close contact with the follicular epithelium, and have a perfectly homogeneous aspect. Langendorff's micro-chemical tests were carried

out upon the gland of the calf and the rabbit, which were hardened in alcohol. Acetic acid caused enormous swelling of the vesicular contents, which were rendered transparent. By washing with 0.6 per cent. NaCl one could restore their former appearance. A 0.2 per cent. solution of HCl also caused this swelling; 33 per cent. KOH or stronger NaOH has the same effect, only to a much less extent. If, now, water be added, rapid breaking up occurs, and only the connective-tissue framework of the glands remains. A 10 per cent. solution of KOH makes the colloid masses indistinct and deliquescent. Strong HNO<sub>3</sub> causes the masses to shrink somewhat; after some minutes a yellow coloration occurs, even in the cold. This reaction (xanthoprotein) comes on almost instantaneously on heating. Addition of ammonia changes the light yellow tinge into an orange. With pepsin, in presence of 0.2 per cent HCl, the colloid masses are soon dissolved. Copper sulphate and KOH at 40° C. give a strong violet tinge to the colloid (Biuret reaction). After many hours in the reagent the colloid masses also give Millon's test. If a section be treated with acetic acid until considerable swelling occurs, and then, after washing, be treated with sulphuric acid, a violet coloration is perceived (Adamkiewicz's reaction).

The colloid masses are not dissolved in boiling water, but are coagulated. The colloid is also coagulated by the other ordinarily used fixing and hardening reagents. These are alcohol, inorganic acids, solutions of metallic salts, and picric acid.

Langendorff considers that the colloid masses are composed either of protein or a substance containing a large proportion of protein. Mucin is not present, as the reaction to acetic acid shows. The protein can hardly be alkali-albuminate, since it coagulates on heating. It may possibly be an alkali albumin modified by containing abundance of sodium chloride. The reactions do not allow of the supposition that any appreciable amount of globulin is present.

The staining power of the colloid is considerable. With picrocarmine the colloid appears bright yellow. If one stains with ammoniacal carmine the colloid takes on the carmine tint very slightly. Eosin and the rest of the

aniline dyes stain the colloid powerfully. After treatment with osmic acid or mixtures containing it, the colloid masses are stained dark; the reduction is particularly marked if one stains for a short time with Ehrlich's hæmatoxylin. After long treatment with logwood the colloid becomes bluish-grey or violet.

Podack (467) agrees with Langendorff in regard to the vacuoles. Hürthle (268, 269) considers them to be artefacts, and is of opinion that the variability in the staining reaction of the colloid depends upon variations in the activity of the gland.

Andersson (7), on the other hand, considers that the appearances referred to by previous authors, as shrinkage products and vacuoles, are in reality globules of a "chromophobe" secretion. Andersson describes also a chromophile secretion.

Schmid (529), in agreement with Langendorff, points out that in osmic preparations the colloid completely fills the vesicles. The vacuoles are thus artefacts.

The concensus of opinion at the present time is that the colloid material arises as a secretion from the epithelial cells lining the vesicle. The epithelium consists of cells having all the characters of true glandular cells, and as in these, the secretion is formed as specific granules in the reticular protoplasm. Details of the process of secretion are given by Langendorff, Hürthle, Schmid, and others.

In the fœtus the structure of the thyroid resembles that of the adult, while in the new-born it is quite different. After birth and for some weeks or months, the vesicles shrivel up and the colloid disappears, and the gland consists of elongated or rounded heaps of epithelial cells, closely pressed together [Méroz-Tydman (391)]. It is possible that this change after birth is pathological [see also Hesselberg (239)].

#### **D. The Intervesicular Cellular Tissue of the Thyroid, and its Significance.**

It has been stated above that "in many lobules one finds in addition to the vesicles solid cords and nests of epithelium cells, and that these are more numerous in the young and developing thyroid." It will be desirable to call particular

attention to this intervesicular material, since its structure and its morphology are of supreme importance as bearing upon the question of the inter-relationship of thyroid and parathyroids.

Schäfer (523), v. Ebner (126), Stöhr (563), Ellenberger (144), and Vincent and Jolly (615), all call attention to this intervesicular tissue. The last-named authors state that in many thyroids there are solid masses of cells, not, however, so distinctly marked off as the parathyroids proper, which are practically identical in structure with the latter bodies. The present writer (455) definitely affirms that this tissue is in all essential respects of the same nature as that forming the parathyroids.

This view has been recently emphasized by Mrs. F. D. Thompson (576). According to this writer, the amount of the intervesicular cellular material varies within very wide limits in the thyroid of different species of animals, in different individuals of the same species, and, to some extent also, in different regions of the same gland. It is not rare to find a pair of vesicles in close juxtaposition to each other, so that the colloid of one is juxtaposed from the colloid of the other by nothing more than two rows of vesicular cells. In other cases there is a certain amount of connective tissue separating the vesicles; but, speaking for mammals generally, it is more usual to find, separating the colloid vesicles from one another, a variable mass composed of cells which are almost identical in size, nature of cytoplasm, size and form of nucleus, with those lining the colloid vesicles. This intervesicular cellular tissue is proportionately much greater where the vesicles are small. This is notably the case in the rabbit, and is also strikingly true in young animals generally (see above, p. 260). In the monkey the amount of intervesicular tissue is proportionately great, and it is not possible to determine any fundamental differences between its cells and those of the vesicles. In the human thyroid there is often as much intervesicular as vesicular material.

This intervesicular cellular substance is shown in Figs. 67-70, 72 and 73.

### E. Structure of the Parathyroids.

The parathyroids in man are built up of closely packed polygonal cells, which are divided up by connective-tissue septa into masses and cords of varying sizes and shapes. The glandules are usually surrounded by their own capsule; but in the case of those placed on the surface of the thyroid, the connective-tissue sheath is seen to be derived from, and continuous with, that of the thyroid lobe. The capsule sends septa into the interior of the organ, which septa convey bloodvessels and nerves destined for the supply of the gland substance.

The protoplasm of the cells often appears to be homogeneous; it does not stain well with eosin, and is vacuolated. The nuclei are spherical and about  $4 \mu$  in diameter, and frequently show a chromatic network. Permeating the whole glandule, and even separating the individual cells in many places, is a delicate network of fine fibres, which appear to be of a distinct nature from ordinary connective tissue [v. Ebner (126)]. It is stained by eosin and faintly also by orcein. Near the periphery of the organ the cells are smaller and lack this special sheath.

In man and different mammals, Kohn (308) distinguishes three different arrangements of the epithelium cells which may be met with: (1) A compact cell mass; (2) a retiform tissue; and (3) a lobular conformation. These different arrangements are not characteristic of any species or any age, but may be found side by side in the same glandule.

In the cat the internal parathyroid has a peripheral layer of cylindrical cells, and there appear to be other differences in structure between this body and the external parathyroid [Kohn (308)]. Thus the cells are not so closely packed in the internal as in the external gland, and their outlines are more easily distinguished. Further, the cell nuclei of the internal parathyroid do not stain so deeply as those of the external body. This last difference, however, can only be detected in adult animals. In some species, as the rabbit, the internal parathyroid is intimately connected with a "central canal" (post-branchial body) and with the thyroid itself (see Figs. 67 and 68).

In close contact with each of the parathyroids we may

find a thymus nodule, and occasionally the central portion of this last is seen to be directly continuous with the tissue of the parathyroid. Again, parathyroids may be found either in the cortex or in the medulla of the thymus gland [Kürsteiner (317)]. When we bear in mind the development of these various organs (see below, pp. 269 and 271), such intimate anatomical connections and occasionally even apparent confusions are not astonishing.

**F. Histology of the Thyroid and Parathyroids considered as One Tissue.**

At first sight the histological features of thyroid and parathyroid appear to be so strikingly different that the majority of authors—at any rate in recent years—have looked upon the two as totally distinct organs. This was the emphatic view of Kohn (308, 309), and it has been shared with more or less modification by nearly all experimental physiologists and pathologists. But, as recently pointed out (576), a careful examination of the glands throughout a series of mammals reveals the fact that the fundamental histological features of the two tissues are, if not identical, at any rate very significantly similar. Some stress has already been laid on the widespread occurrence of intervesicular cell masses in the thyroid, whose cells are of the same character as those lining the vesicles; and the view of several recent investigators is that the essential elements of thyroid and parathyroid are the same. This only becomes clear when a large number of animals is studied; for occasionally one sees parathyroids or portions of parathyroids which, from their degree of compactness, staining reaction, and encapsulation, present an appearance markedly different from that of the parenchyma of the thyroid.

Sometimes the parathyroid nuclei are slightly smaller than those of the thyroid tissue; sometimes they are slightly larger. Again, in some instances, they appear more closely packed than in the thyroid, while in others they are less closely packed. These differences are, however, not fundamental [Thompson (576)], and there are abundant instances where it is almost impossible to distinguish the parathyroid from the intervesicular tissue of the thyroid.



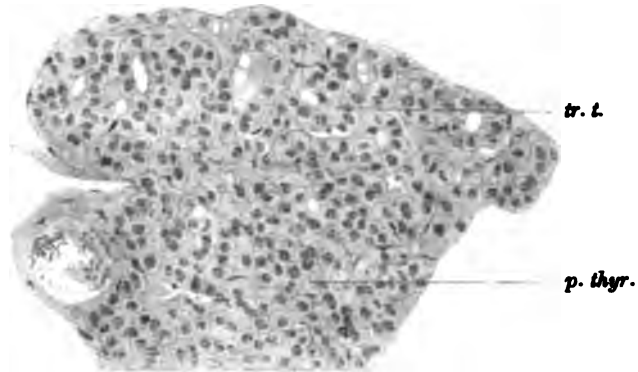


FIG. 67.—Rabbit. The figure shows an undoubted transition between thyroid (upper part of figure) and internal parathyroid (lower part of figure).

*p. thyr.*, parathyroid ; *tr. t.*, transition between thyroid and parathyroid.



FIG. 68.—Shows a similar appearance to that represented in Fig. 59.

*thyr.*, thyroid ; *p. thyr.*, parathyroid ; *tr. t.*, transition between thyroid and parathyroid.

This is specially true in the case of the internal glandule, which, as admitted by Kohn, is often in direct continuity with the thyroid, and which may be frequently observed to show every kind of transition to the colloid vesicular formation of the latter. This transition from thyroid into para-



FIG. 69.—Parathyroid of the ox. This preparation was made from a nodule of glandular tissue lying outside the thyroid gland in the position where the external parathyroids are usually found. It is obvious that the structure is of a mixed nature, revealing every kind of intermediate formation between thyroid and parathyroid.

*bld. c.*, blood-corpuses ; *c. ves.*, colloid vesicle ; *p. thy.*, parathyroid.

thyroid is sometimes very distinctly seen in the rabbit's gland (see Figs. 67 and 68).

More striking illustrations are described and depicted by F. D. Thompson (576) in the case of the ox (Fig. 69) and the badger (Fig. 70). In the latter animal there is, so far as can be perceived, no kind of difference as regards size

and shape of nuclei or their staining reactions, in compactness or general arrangement between the two tissues. The impression given is that the only difference consists in the presence of colloid in the thyroid. If, indeed, in any part

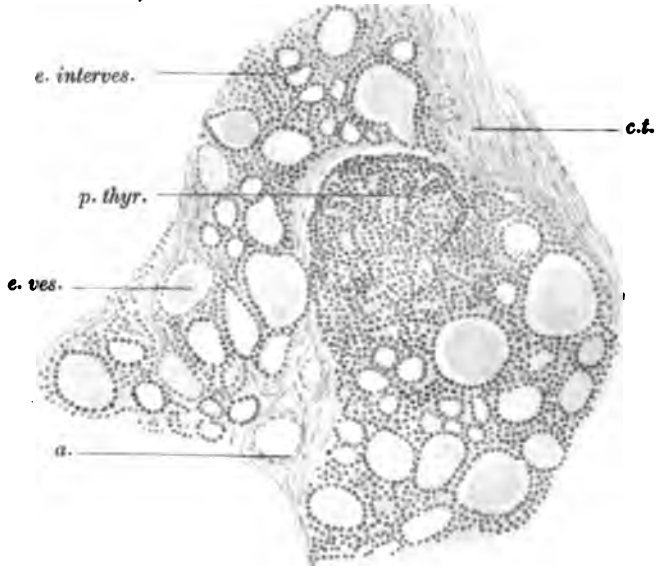


FIG. 70.—Badger. Internal parathyroid. The section is taken through that portion of the parathyroid which becomes continuous with the thyroid. It is evident from the drawing that there is no line of demarcation between the two organs, and, further, that the details of structure gradually change in the passage from one to the other.

*a.*, artery ; *c.t.*, connective tissue ; *c. ves.*, colloid vesicle ; *e. interves.*, inter-vesicular epithelium cells ; *p. thy.*, parathyroid.

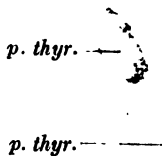


FIG. 71.—Human. A drawing, as seen under a simple lens, of a portion of the thyroid and a parathyroid which is considerably hypertrophied and otherwise modified. The specimen is pathological, but there is no record of the patient. The object of this figure is to show that the structure in question is in reality morphologically and topographically a parathyroid.

*p. thy.*, parathyroid ; *thy.*, thyroid.

of the parathyroid a spherical droplet of colloid were to be formed among the cells, this portion of the glandule would have to be called thyroid, and the circle of cells immediately surrounding the colloid would be regarded as the lining

epithelium of the thyroid vesicle. This, in point of fact, actually occurs under certain circumstances ; Figs. 71, 72, and 73, taken from Mrs. Thompson's paper (576) illustrate

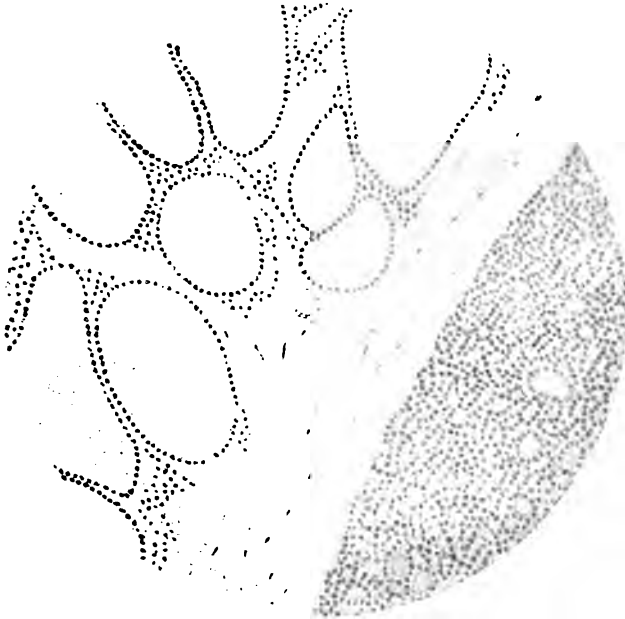


FIG. 72.—From the same preparation as Fig. 63. A portion of the thyroid and neighbouring parathyroid, with a fairly thick connective-tissue partition ; low power. On the right we see the colloid vesicles of the thyroid ; on the left the parathyroid, which is of a typical parathyroid structure near the connective-tissue septum ; but which shows several undoubted colloid vesicles in the left-hand portion of the drawing.

this very clearly. The drawings represent what topographically is, or, to be more correct, *was*, parathyroid ; but many parts of the substance are studded with colloid vesicles.

### G. Development of the Thyroid.

The thyroid is the chief of the organs arising from, or in close topographical relation to, the gill-clefts. Other organs in the same group are the thymus, the parathyroids, the post-branchial bodies, and the branchial bodies of the Anura.

The origin of the thyroid is practically the same throughout vertebrates. It arises from the ventral wall of the pharynx in its anterior region, as an unpaired outward pro-

jection of epithelium [Remak (483)]. As stated above, in *Amphioxus* and *Ammocœtes*, the opening into the buccal alimentary tube remains patent, and the thyroid appears to be an organ of very ancient origin, which shows relationship to the hypobranchial furrow of *Tunicates* [W. Müller (416)]. In *Petromyzon* the organ detaches itself completely from its place of origin, the opening becomes closed, and a number of closed vesicles are formed, lined with cylindrical epithelium, and containing colloid [Schneider (530)].



FIG. 73.—From the same preparation as Figs. 63 and 64. A small portion of the parathyroid shown in the last two figures. This section is from a part of the parathyroid somewhat further removed from the thyroid than any part of Fig. 64. The drawing was made with a camera lucida; high power. It is seen that the vesicles, although small, are typically thyroidal in character. They may be compared with those from the rabbit, shown in Fig. 67.

*end.*, endothelium; *c. ves.*, colloid vesicle.

In fishes the organ remains unpaired, but in *Amphibia* it divides into two portions, whose position differs in different species.

In the *Sauropsida* the origin of the thyroid is very similar. The stages have been worked out in the adder, tortoise, and crocodile by v. Bemmelen (30, 32, 33), in *Anguis* by Prenant (470, 471, 472), in *Lacerta* by de Meuron (392, 393), v. Bemmelen (30, 32, 33), and Maurer (375), and in *Hatteria* by Dendy [quoted by Maurer (376)].

The original vesicle becomes a compact organ, and in *Lacerta* becomes developed into a bilobed organ with a median isthmus. In the interior one can for a long time trace a lumen which is the remains of the aperture of the original vesicle. This is lined with cylindrical epithelium. The

In all vertebrates above the *Cyclostomata* the unpaired rudiment of the thyroid arises as an evagination of the floor of the pharynx between the bases of the first and second branchial arches. The structure then separates itself completely from its original point of growth, and appears as a closed vesicle. In fishes the organ remains unpaired, but in

colloid-containing vesicles do not, however, communicate with a canal.

In birds the two lobes become quite separate.

The origin of the thyroid in mammals has been, and still is, a matter of considerable controversy. There can be no doubt about the median rudiment, which arises in the same way as in other vertebrates—*i.e.*, as an evagination of the floor of the pharynx between the first and second branchial arches. In the human embryo [His (244)] the evagination is a small pouch beginning to expand laterally in an embryo of 5 millimetres in length; in an embryo of 10 millimetres the lateral expansion has much increased, and there is a median duct, the opening of which upon the surface of the tongue corresponds to the *foramen cæcum*; the duct itself is known as the *ductus thyreo-glossus*. The whole structure now consists of a bilateral epithelial vesicle connected by a slender hollow pedicle with the surface of the tongue. The duct persists up to the eighth week, gradually elongating as the thyroid and the tongue separate. The duct usually begins to be obliterated during the fifth week, but sometimes persists. After the fifth week the vesicular portion expands rapidly.

The development in other mammals does not call for a separate description.

Many authors [Wölfler (644), Stieda (562), Born (55)] describe a lateral rudiment in addition to the median, and this is accepted as the true account by the authors of some textbooks [*e.g.*, Minot (397)], but this lateral rudiment appears to be that of the post-branchial body (*vide infra*, p. 270).

In most mammals the thyroid remains a single organ, consisting, as in man, of two lobes, with a connecting isthmus. In some, however, the right and left lobes are completely separate. The colloid does not begin to be formed in mammals till towards the end of foetal life, and sometimes even not till after birth.

But before going further it will be necessary to give some account of the *post-branchial bodies*, which are present in all Gnathostomata except Heptanchus and Teleosts.

In Selachii the organ was first observed by v. Bemmelen (31), who called it the "suprapericardial body." He describes it as an evagination of the ventral wall of the pharynx

*behind the last gill-cleft.* This becomes separate from the wall of the pharynx, and now consists of a vesicle lined with epithelium cells. It bears some resemblance to the original rudiment of the median thyroid, and soon consists of a mass of separate vesicles. Whether these contain colloid is not known.

In Amphibia, Reptilia, and Aves, the post-branchial body is formed as an evagination behind the last gill-cleft, sometimes, however, only unilaterally. In these classes of animal the vesicles never contain colloid.

In mammals Wölfler (644) and Stieda (562) considered that the paired post-branchial bodies are the original material out of which the thyroid body is formed. These two authors investigated the question in the pig, sheep, calf, and rabbit, and concluded that there is no median rudiment at all. Born (55) considered that the mammalian thyroid is made up partly from the median rudiment, and partly from the paired post-branchial bodies. But this has recently been denied by Verdun (600, 601, 602), who believes that the thyroid is derived exclusively from the anterior (median) rudiment. This appears to be certainly true for the lower vertebrates (Maurer). Verdun further believes that the post-branchial bodies, even if they become united with the median rudiment of the thyroid, always have a different structure.

Of peculiar interest are the researches of Maurer (374) upon Echidna. In this animal, as in all vertebrates, the post-branchial body arises behind the fourth gill-cleft, and soon develops into a gland having a structure like that of the thyroid, the important point being that *colloid is contained in the vesicles.* In Echidna these post-branchial bodies (colloid glands) never unite with the thyroid proper, which is a large gland, with two lobes and a connecting isthmus.

In other mammals the post-branchial bodies may assume a structure identical with that of the median thyroid. How much, if any, of the fully developed thyroid is derived from the post-branchial bodies still remains an open question [see Verdun (604), Maurer 376)].<sup>1</sup>

<sup>1</sup> For a recent account of the post-branchial body in the human subject see Sophia Getzowa (182).

### H. Development of the Parathyroids and some other Branchial Cleft Organs.

The development of the thymus will be treated hereafter (p. 353), but it will be convenient in this place to deal with the development of the parathyroids and the thymus nodules found in connection with the thyroid.

The particular gill-clefts with which we are at present specially concerned are the third and fourth.

From the epithelium on the ventral aspect of the third cleft arises the main portion of the thymus. This may be called "thymus III." (see Fig. 74, p. 272). The ventral proliferation of the epithelium of the fourth cleft also gives rise to thymus tissue, but this is usually simply a small nodule in the substance of the thyroid, and is called "thymus IV."

The dorsal aspects of the third and fourth clefts show thickenings of the epithelium which, however, do not develop into thymus tissue, but retain a typical "epithelial" structure. These are the parathyroids named respectively "parathyroid III." and "parathyroid IV." In connection with the last is found a cavity lined with epithelium. This is the post-branchial body.

The thymus nodule sometimes found in close relation to the external parathyroid ("parathyroid III.") is simply an isolated portion of the main thymus ("thymus III.>").

The accompanying diagrams [from Kohn (309)] will help to make the matter clear (Figs. 74, A and B).

### I. Diseases of the Thyroid and Parathyroid.<sup>1</sup>

This part of the subject will only be treated briefly, and in such a manner as to utilize, so far as possible, the facts which have been accumulated in regard to diseases of the thyroid and parathyroids, in order to explain the functions of these organs.

Thyroiditis acuta, carcinoma, sarcoma, syphilis, tubercu-

<sup>1</sup> The word "parathyroid" is included in the title of this section, although no diseases of this organ are here specifically referred to, because, in the opinion of the present writer, several of the diseases of the thyroid-parathyroid apparatus may involve disease of the parathyroid, and several of the symptoms supposed to be due to lesions of this glandule may really be due to disease of the thyroid. A further discussion of "tetany" in relation to the parathyroids will be found in a later section of this work (see p. 304).



## THE DUCTLESS GLANDS

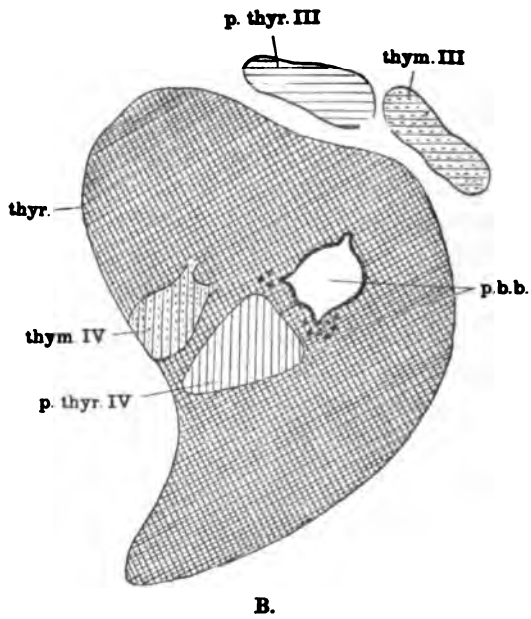
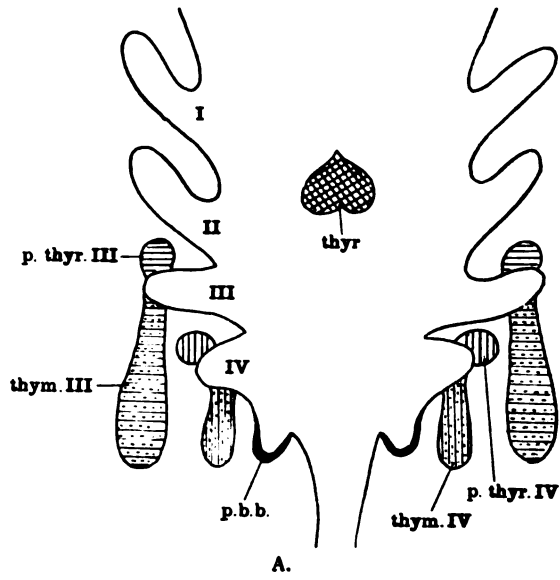


FIG. 74.

losis, and echinococcus are all known, but apparently none of these lesions give rise to any of those symptoms usually associated with absence of thyroid function—viz., myxœdema, tetany, etc. This seems to be the case even when gangrene occurs [Lebert (326), Ewald (153)].

The diseases which will be referred to are—(1) Goitre, (2) endemic cretinism, (3) myxœdema, (4) cachexia strumipriva, (5) Graves's disease, and (6) endemic tetany.

1. *Goitre.*

The ætiology of endemic goitre is a long-standing puzzle, and there are many aspects of the question which still remain in obscurity. The distribution of the disease is so extraordinary and so well known that it need not be described here. It is now generally recognized that it is an infection due to a living germ confined to certain geological formations, and transmitted to man by means of drinking-water [Ewald (153)].

McCarrison (379, 380, 381, 382, 383, 384), from observa-

EXPLANATION OF FIG. 74.

(Diagrams A and B.)

A illustrates the development of the branchial organs of mammals, B shows their actual relations in the adult.

The different related rudiments of the same branchiomere are represented by a similar direction of shading lines; so also the corresponding organs. Thus the rudiments from the third cleft are represented in A by horizontal lines, as also the organs thus arising in B. The rudiments and organs from the fourth cleft are characterized by vertical lines. The post-branchial body is shown in thick outline, the thyroid by crossed lines.

The different kinds of tissue arising from one and the same branchiomere are indicated by differences in the shading. The parathyroid tissue is shown by lines, the thymus tissue by alternate continuous and interrupted lines. The post-branchial body is represented in the developed condition as a hollow space with several glandular nodules (shown in dark circles).

A shows the four internal gill slits (I. to IV.), the epithelial origins of the parathyroids (*p. thy.* III., *p. thy.* IV.), the origin of the thymus (*thym.* III., *thym.* IV.), the rudiment of the thyroid (*thy.*), and that of the post-branchial body (*p.b.b.*).

B represents a schematic transverse section through the fully developed thyroid (at about the level of the junction of the upper and middle third of the thyroid lobe of a cat). The lettering corresponds to that in Diagram A. The structures which arise from the third cleft become the "external" parathyroid and thymus nodule (separated fragment of thymus III.); those which arise from the fourth cleft become the "internal" parathyroid and the thymus nodule (*p. thy.* IV., and *thym.* IV.). The post-branchial body is surrounded by thyroid tissue.

[A is after Groschuff (204) in ruminants; B from Kohn (309) in the cat.]

tions carried out in Gilgit, Kashmir, concludes that goitre can be experimentally produced in man by the administration of the matter in suspension separated by filtration from waters that are known to be goitre-producing. Goitre cannot be produced when the suspended matter is boiled. The disease is due, therefore, not to mineral, but to the living component of the suspended matter—in other words, to a living organism of disease. The incubation period of experimentally produced goitre is usually about ten to fifteen days. Goitre can be cured by the administration of intestinal antiseptics. Thus the lactic-acid ferments exercise a curative action when applied to the treatment of incipient goitres. It is probable, therefore, that the organism which is the cause of the disease is parasitic in the human intestine. The fæces of most cases of goitre in Gilgit show a plentiful amœbic infection, but whether the disease is due to this infection has not been determined. The disease cannot be communicated to dogs by means of extracts from the fæces of goitrous individuals [McCarrison (384)]. Bircher (44) finds that filtering does not destroy the contagion, while boiling does.

Some interesting experiments have been performed by Guthrie and Ryan (211) upon alterations of the circulation in goitrous thyroid glands in dogs. They record that when the circulation is reversed in the inferior thyroid vein by anastomosing this vein with the central end of the common carotid artery, there is marked decrease in size of the lobe on the operated side.<sup>1</sup>

Sporadic goitre appears to be of quite a different nature.

## 2. *Endemic Cretinism.*

The precise relationship between goitre and cretinism has been the subject of much discussion and speculation [see Virchow (618, 619), Fodéré (162), Lombroso (340, 341), Ewald (153)].

The subject has recently been reinvestigated by McCarrison (382) in the Chitral and Gilgit Valleys. He concludes that

<sup>1</sup> Other recent papers on goitre are : Reich (481), Ewald (154), Wilms (641), Davidsohn (115), Ullmann (588), Carpi (78), Müller (416), Handmann (227), Hutt (277), Marine and Lenhart (364), Kloeppel (299), Isenschmid (280), Blauel (48), Sanderson-Damberg (513).

the degree to which cretinism is associated with goitre is determined by the age of the endemic, and varies directly with the extent to which the latter disease prevails among the adult population. Cretinism is rarely, if ever, due to the development of a goitre in the individual. The thyroid enlargement is, or may be, an effect ; it is not the cause of the disease. Defective thyroid function in the mother is the essential factor in the production of cretinism.

Cretinism is due to the action of toxic agents, notably that of endemic goitre, on the developing thyroid of the unborn child. The thyroid defect is congenital, but it may remain latent pending its manifestation through the impulse of some accidental circumstance. The defect in cretinism is one of the whole thyroid mechanism, of the parathyroids as well as of the thyroid gland. The diversity of symptoms is due to the extent to which the defect bears on the whole or part of that mechanism [McCarrison (382)].

The symptoms of cretinism have been so often and so fully described that it is unnecessary to make more than a brief reference to some of them. The changes in the skin are stated by many observers to be identical with those found in myxœdema, but Scholz (535) cannot confirm this.

McCarrison (382) states that in the Chitral and Gilgit Valleys there are two distinct types of the disease—(1) the myxœdematous type, and (2) the nervous type. Cases commonly present the clinical features of a combination of these. Deaf-mutism is an almost constant accompaniment of both types of the disease. The myxœdematous type corresponds with the form met with in Europe.

The nervous cretins are helpless, and usually deaf and dumb. There is a "knock-kneed" spasticity of the lower limbs, increased knee-jerk, and there may be marked flexion of the toes on the sole. The upper limbs assume a position of right-angled flexion ; the thumb may be drawn into the palm and the fingers closed over it, whilst the wrist is flexed. Among other nervous symptoms are movements of the head, grimaces, convulsions, nystagmus, and internal strabismus, and idiocy. It is important to note that these nervous cases are considerably benefited by treatment with sheep's thyroid. This would be explained by many modern writers by the presence of parathyroid

tissue in the glands employed for administration. It appears to the present writer that the results obtained lend support to the view, urged from other considerations in various parts of this work, that thyroid and parathyroids together form one apparatus. This view is the one adopted by McCarrison.<sup>1</sup>

### 3. *Myxœdema.*

(a) *Symptomology.*—In 1874 Sir William Gull (164) communicated to the Clinical Society of London a paper bearing the title, "On a Cretinoid State supervening in Adult Life in Women." This account was based upon five cases. In 1877 Ord (437) proposed the name "myxœdema," which has ever since been employed. This writer describes changes in the thyroid. Curling (107) and Fagge (155) had previously described atrophy of the gland in cretinism. The early history of the subject may be completed by referring to the work of Charcot (80), who called the disease "cachexie pachydermique"; Savill (521), who first described a case in a male subject; and Hadden (213), who first definitely ascertained that atrophy of the thyroid is commonly associated with myxœdema. [See also Report of Myxœdema Committee of the Clinical Society, 1888 (484).]

The ætiology of myxœdema is obscure. Heredity, traumatism, tubercular family history, alcohol, syphilis, and many other factors have been alleged. The disease is chronic, and the onset is very gradual.

In most cases myxœdema shows itself in a gradual swelling of the skin. This may be accompanied by nervous disorders, neuralgia, convulsions, "tetany," mental disturbances, and skin diseases. The swelling of the skin is at first most noticeable on the face. The chin, eyelids, nose, lips, and cheeks swell up, and the palpebral cleft is narrowed. A slowly increasing languor is often felt in early stages, and a sensitiveness to cold is frequently noticed. Headache is an early symptom in some cases.

The skin may become yellowish, and shows in fully developed cases what is called "solid œdema." The swelling resembles œdema or fat, but on palpation feels softer

<sup>1</sup> See also Flinker (161), Biroher (45, 46).

and more elastic than fat, and unlike ordinary œdema, it does not pit on pressure, nor does any fluid exude if the skin is pricked. The weight of the patient is increased very considerably. The skin is wrinkled in some regions, pendulous in others. The swelling is fairly uniform over the trunk and limbs, but is most noticeable in the hands and feet. The skin becomes dry and rough and cold. In later stages of the disease perspiration may be entirely absent. Warts and moles may occur.

The hair becomes thin and scanty. In some cases the head is almost completely bald, and the skin of the scalp becomes dry, brown, and scaly. The teeth often become brittle and carious. The mucous membranes may be swollen, and there is dryness in the mouth and nose. In fully developed cases the temperature is almost continuously one, two, or three degrees below normal. Mental dulness, drowsiness, and slowness of reaction are characteristic of most marked cases. There may be hallucinations going on to definite insanity. Sight, hearing, taste, and smell are often more or less impaired, and sexual feeling may be diminished.

We shall see later on (p. 279) how far these symptoms correspond with those observed in human beings after operations upon the thyroid, and in animals after experimental thyroidectomy (p. 286).

(b) *Morbid Anatomy*.—The most interesting changes are found in the thyroid lobes. The Myxœdema Committee in 1858 (484) found that out of fifteen cases in which the thyroid was examined post mortem, there were six of atrophy of the glands, and all were diminished in size, of a pale yellowish-white colour, hard, and fibrous. There was a connective-tissue overgrowth which led to a destruction of the parenchyma. At the same time there was a new formation of lymphatic tissue.

Similar conditions have been reported by Buchanan (61), Hun and Prudden (270), Hale White (636, 637, 639), Barling (19), Urquhart (590), and Hirsch (243). Hanau (225) found that such vesicles as were still present were filled with cell débris and colloid substance. V. Eiselsberg (141) reported that the cells of the vesicles were reduced in number and their nuclei in staining capacity. The

intervesicular tissue was œdematous and poor in nuclei and in fibrils.

The pathological process consists of a very slowly progressive atrophy. In most cases this seems not to be the result of ordinary inflammatory processes, though Ponfick (469) records diminution in size of the thyroid as a result of a violent interstitial inflammation. Even when the thyroid is increased in dimensions, as occasionally happens, the vesicular substance has for the most part disappeared, and its place has been taken by interstitial growth.

In the skin the connective tissue of the corium has its elements torn asunder. The fibres are hyperplastic. The cell nuclei and the fibrils of the gelatinous substance between the fat lobules are multiplied. The whole tissue has a transparent appearance. It is as if the skin were saturated with a semi-fluid substance. Ewald (154), Hirsch (243), and Cushier (108) have found peculiar, glistening, highly refractive bodies, whose nature is not known. A similar condition is reported in other organs and tissues.

The chemical nature of the infiltration is not certainly known. It is very doubtful whether it is mucin, and there are many reasons for thinking that it has not the composition of ordinary œdema. Cases in which a chemical examination of the skin can be carried out are so rare that it will probably be many years before the matter can be satisfactorily settled. The papers of Ord (437), Hun and Prudden (270), Halliburton (215, 216), and Kräpelin (313) may be consulted. Ewald (153) thinks that there is a trophic change in the direction of degeneration of fatty tissue or a persistence of the embryonic mucous tissue.

(c) *Pathogeny*.—In the view of perhaps the majority of physicians and pathologists who have studied the subject, the pathogeny of myxœdema is very simple. Thus, Murray (422) says: "These facts clearly show that myxœdema in man is entirely and solely due to disease or removal of the thyroid gland and the consequent failure of the supply of its internal secretion." We have seen (pp. 131 and 134) that in the case of Addison's disease it is difficult or impossible to produce artificially the symptoms of this disease by extirpation of the adrenals in animals. The most striking of all the symptoms—namely, pigmentation of

the skin, does not occur in the operated animals. Similarly we shall see (p. 301) that in animals deprived of their thyroids swelling of the skin and subcutaneous tissues is, at any rate, not a common symptom, and according to some observers cannot be induced at all. It must be remembered, however, that it is scarcely possible to imitate artificially the exceedingly gradual fibrosis and destruction of glandular tissue which occurs in myxœdema.

The parathyroids are intact according to the majority of observations, but there is some evidence that the pituitary body may be concerned [Schilder (528)].

#### 4. *Cachexia Strumipriva.*

In 1882 Reverdin (485) described the results of goitre extirpation. In the following year Kocher (301) published his classical report on eighteen cases. Later in the same year J. and A. Reverdin (486) noted the resemblance of the symptoms to those described by Gull, and hence called the condition "operative myxœdema." Kocher's term was "cachexia strumipriva." "Cachexia thyreopriva" is a more correct term, but is less usually employed.

It is important to note carefully the symptoms recorded when the thyroid is totally removed from the human subject. The cachexia comes on at a very variable period after the operation—from six to eight days up to months or years. Patients advanced in years suffer less than young people under twenty. The patients first complain of fatigue, weakness, and heaviness in the limbs, sometimes associated with pains, tremblings, and sensations of cold. There is a diminution of mental activity, loss of memory, slowness of thought, speech, and movements. Then one notices fugitive swellings of the face, hands, and feet, which gradually become stationary and lead to a coarseness and puffiness of the whole body. The skin loses its suppleness, and becomes infiltrated, dry, and scaly. The hairs of the head fall out.

There are also nervous symptoms, such as are observed in myxœdema. The symptoms, in fact, as they were described by Kocher and Reverdin [also by Baumgärtner (26, 27, 28) and Bruns (60)], are very much like those of myxœdema, except, perhaps, that not so much stress is



laid on the "solid œdema." More recent descriptions have been given by Albert (3), Weiss (626), Reverdin (487), Szumann (572), Higuët (241), and Schramm (538, 539).

The majority of writers since the year 1896 have assumed that the precise nature of the symptoms depends on the amount of injury inflicted upon the parathyroid bodies—in other words, that myxœdema properly so called is due to the absence of thyroid functions, while the nervous symptoms (tetany) are due to injury to the parathyroids. This matter will be referred to again when extirpation experiments on animals are dealt with.

##### 5. *Graves's Disease (Exophthalmic Goitre, Basedow's Disease).*

The three cardinal symptoms of this disease are palpitation, exophthalmos, and increase in size of the thyroid gland. Some authors consider that certain nervous symptoms are equal in importance with those here mentioned.

With regard to the pathology of Graves's disease, it has been discussed whether the primary lesion is in the nervous system or in the thyroid gland. There are certainly changes in the thyroid, though it is not yet absolutely certain that these are constant. It has been shown by Halsted (220, 221) and Edmunds (134) that if a portion of the thyroid be removed from an animal, the remainder shows certain peculiar changes, described as compensatory hypertrophy. The vesicles become irregular or stellate in shape, the lining membrane is folded, the epithelium is proliferated, and the micro-chemical reactions of the secretion are altered so that it stains badly. Now, these changes are practically identical with those found in Graves's disease. According to Marine (359, 360), an enormous proportion of stray dogs in Cleveland, Ohio, are thus affected, though they do not show the symptoms of exophthalmic goitre. Dr. Marine has, however, observed that if these dogs be treated with iodides, the alveoli again become rounded and filled with colloid, and, according to Kocher [quoted by MacCallum (349)], the administration of iodine will prevent the development of the folded condition after the operative extirpation of part of the thyroid.

The most generally accepted theory as to the pathology of exophthalmic goitre is that the disease is due to over-activity on the part of the thyroid, that an excess of thyroid secretion is poured into the circulation. But Oswald [quoted by MacCallum (349)] believes that we have, in fact, a condition of thyroid insufficiency, since the gland is often empty of colloid, and contains relatively little iodine-holding secretion. MacCallum (349), on the other hand, states that the removal of part of the thyroid improves the condition of the patients, and the administration of thyroid extract makes them worse. The benefit of surgical treatment is urged by several surgeons [Shepherd (546)]. Marine and Lenhart (361) do not believe that the thyroid changes in exophthalmic goitre are either primary or specific, or that the thyroids in these cases produce an increased amount of a physiologically active secretion. On the other hand, they think that the thyroid changes are always secondary to some more fundamental cause, and that there is a hypersecretion quantitatively, but a hyposcretion qualitatively (physiologically); and, lastly, that the usual final stage of all cases, unless terminated by death or relative recovery, is myxœdema.

Reid Hunt (271) has recently found that when small amounts of thyroid are administered to mice for a few days the animals acquire markedly increased resistance to poisoning by acetonitrile. This is believed to be an exceedingly delicate test for thyroid substance. It was found, moreover, that it required nearly twice as much acetonitrile to kill mice which had been fed upon blood from a case of exophthalmic goitre as it did to kill those which had received normal blood. This experiment, Hunt believes, shows that the blood of patients suffering from exophthalmic goitre contains an excessive amount of thyroid secretion.<sup>1</sup>

<sup>1</sup> Other recent papers on exophthalmic goitre are: Syllaba (571), Chvostek (83), Mendel (389), Wolfsohn (646, 647), Holmgreen (255), Hasselwander (232), Iscovesco (279), Gley (197), Kocher, Th. (303), Kocher, A. (304), Otto (444), Sanger u. Sudeck (520), Kappis (294), Mitchell (400), Kreeke (316), Mayerle (378), Parisot (450), Hale-White (638).

### 6. *Endemic Tetany.*

Endemic tetany, as it occurs in Europe, seems to be a disease of large cities, usually appearing in the spring ; it has a tendency to assume epidemic proportions, and it is very local in its distribution.

In India there is an endemic tetany in rural districts. Attention has been specially called to this affection by McCarrison (385).

The distribution of tetany in India is peculiarly local, and appears to correspond more or less with the distribution of goitre. Sufferers from tetany appear to be able to rid themselves of it by going to a locality where it does not prevail.

In India tetany is a disease of child-bearing women, and there is a marked family tendency to the disease. The children of women who suffer from tetany are frequently cretinous.

Menstruation appears to increase the frequency and the severity of the attacks of tetany, especially so when this function is in any way disordered.

The seasonal prevalence of tetany—its practical limitation to the spring months—is very striking. “Chill,” fright, and mental distress often provide the stimulus which produces the spasms. The patients are nearly all goitrous, and incomplete myxœdema may be present.

McCarrison finds thymol very useful in treatment, and this affords proof of the now generally accepted opinion that the spasms of tetany are due to the action of toxic substances absorbed from the alimentary canal. Goitre is an important cause of tetany, because it reduces the efficiency of the thyroid gland. The author discusses the question of the parathyroids as being a possible seat of the lesion in tetany, but he does not favour the view that parathyroid deficiency is the cause of the disease. He considers the thyroid apparatus as a whole responsible for protecting us from such maladies as myxœdema and tetany. In order to study the subject to best advantage it is suggested that, after thyroidectomy or parathyroidectomy, those animals should be rejected as unsuitable in which signs of tetany or other untoward accident have developed, and those only

should be selected for observation in which no apparent ill-effect has been produced. Then the action of various poisonous products should be tested on the selected animals, controlling the results by similar observation on healthy animals of the same species. Such a line of research would not fail to throw some further light on the ætiology of tetany [McCarrison (385)].<sup>1</sup>

### J. Early Views as to the Functions of the Thyroid.

According to Handfield-Jones (226), Galen does not give any very distinct account of the thyroid, but seems to allude to it in his work "On the Use of the Parts of the Human Body." In speaking of the glands of the larynx, he says these "are always found more loose and spongy than others, and which, by the common consent of anatomists, have been created for the purpose of moistening and bathing all the parts of the larynx and the passage of the throat." Morgagni (408) also quotes the following, which shows that Galen was informed of the absence of a duct: "Now, the neck has two glands in which a moisture is generated. But from the two glands which are in the neck there come forth no vessels by which the moisture may flow out, as those do from the glands of the tongue."<sup>2</sup>

Wharton (633), in 1656, gives a good account of the anatomy of the thyroid and notes that "it is much more full of blood than any other gland, also more viscid and solid, and more resembling muscular flesh. This is the only difference, that it is not of a fibrous structure but rather of a glutinous nature."<sup>3</sup> He allots four functions to the gland: "(1) The first and principal use of these glands appears to be to take up certain superfluous moistures from the

<sup>1</sup> The following is a list of additional papers on the pathology of the thyroid: Turin (584), Kostlivy (310), Sumita (569), Marchiafava (358), Siegmund (547, 548), Robertson (490), Higbee and Ellis (240), Mallinrodt (356), Levi (334), Kehler (296, 297), Josefson (291), Mayer (377), Levi et de Rothschild (335).

<sup>2</sup> "Collum autem habet duas glandulas in quibus generatur humiditas. Sed ex duabus glandulis quæ sunt in collo, non veniunt vena in quibus currit humor, sicut proveniunt ex duabus glandulis linguæ" (Galen, Tract. 2.)

<sup>3</sup> "Quod ad carneam earum substantiam spectat, ea multo majis sanguinea est, quam cujusvis alius glandulæ; viscidior quoque, solidiorque ac similior carni musculosæ. Hoc solummodo interest quod non sit fibrosa, sed potius glutinosa" (Wharton, *loc. cit.*).

recurrent nerve, and to bring them back again into the vascular system by their own lymph channels. (2) To cherish the cartilages to which they are fixed, which are rather of a chilly nature, by their own heat ; for they are copiously supplied with arteries, and abound with blood, from whence they may conveniently impart heat to the neighbouring parts. (3) To conduce by their exhalations to the lubrication of the larynx and so to render the voice smoother, more melodious, and sweeter. (4) To contribute much to the rounded contour and beauty of the neck ; for they fill up the empty spaces about the larynx, and make its protuberant parts almost to subside and become smooth, especially in the female sex, to whom on this account a larger gland has been assigned, which renders their necks more even and beautiful."

The third function, it will be noted, is only Galen's view more definitely formulated. This theory, in one form or another, long remained in vogue.

Verheyen, in 1720, says : "This gland, beyond doubt, serves also to moisten the neighbouring parts ; but, because it is very large, there is an apparent reason why it should have rather large excretory ducts, or one at least very conspicuous, which yet hitherto has not been discovered."

Morgagni (408) is undecided whether or no the gland has a duct. He describes vesicular cavities in enlarged thyroids, and these he correctly supposed to be the normal vesicles ("natural cavities") distended by the accumulation of their secretion. He is inclined to think that there must be a duct opening into the pharynx or the trachea.

Santorini (518) fails to find a duct, but still thinks that the thyroid gland may be forced to expel its secretion by the contraction of the overlying muscles and other causes.

Haller (214), in his textbook, written in 1776, after discussing the anatomy of the gland and detailing the fruitless attempts to discover an efferent duct, says : "Alii Cl. viri, cum penitus de inveniendō ductu desperassent, ad aliam omnino utilitatem se converterunt. Liquorem peculiarem in ea glandula parari, qui receptus venulis sanguini reddatur, quæ lienis et thymi fit utilitas, ipse Ruyschius (512) autumavit."

Thus, in the year 1776, we have the thyroid, the thymus,

and the spleen classed together as glands without ducts, which manufacture a special fluid, which is received into the veins, and so returned to the general circulation. This, so far as it goes, and, so far, at any rate, as it refers to the thyroid, is not far different from the modern conception.

Although from this time on the glandular nature of the thyroid was universally conceded, and there was much speculation as to the precise mode of secretion and the elimination of the product from the vesicles into the circulation, yet the active function of the secretion itself was for a long period not the subject of any serious inquiry, and, indeed, the possibility of its being of any great importance in the economy was scarcely suspected. Thus, Cruveilhier (104), in 1834, states that the use of the secretion of the thyroid is unknown,<sup>1</sup> and about this time Sir A. Carlisle<sup>2</sup> supposed that the gland forms a protection to the delicate organs of the voice, against the variations of the external air.

In 1844 Simon (552) put forward a very interesting theory in regard to the function of the thyroid, all the more interesting as it has quite recently been revived and developed by Stahel (558), Waldeyer (622), and Cyon (109). Simon considered that the thyroid exercises a regulatory function on the blood-supply to the brain, exerting also its secretory function in an alternating manner with the substance of the brain. "What diversion is to the stream of blood viewed quantitatively, alternative secretion would be to the composition of the blood viewed qualitatively; and I should conceive that the use of the thyroid gland, in its highest development, may depend on the joint exercise of these two analogous functions. I should suspect not only that the thyroid receives, under certain circumstances, a large share of the blood which would otherwise have supplied the brain, but also that the secretion of the former organ bears some essential relation (which chemistry may here-

<sup>1</sup> "L'absence de conduit excréteur doit-il faire rayer la glande thyroïde du nombre des glandes de l'économie? Je suis loin de le croire. Je pense qu'il existe dans l'économie des glandes sans conduits excréteurs, tels que le thymus, la capsule surrénale et la glande thyroïde. Le liquide produit dans l'intérieur de la glande est absorbé en entier, et remplit des usages inconnus" (Cruveilhier, *loc. cit.*).

<sup>2</sup> Quoted from Handfield-Jones (226).

after elucidate) to the specific nutrition of the latter ; that the gland—whether or not it appropriates its elements in the same proximate combination as the brain does—may, at all events, affect in a precisely similar degree the chemical constitution of the blood traversing it, so that the respective contents of the thyroid and cerebral veins would present exactly similar alterations from the characters of aortic blood. Finally, I should suppose that these actions occur only or chiefly during the quiescence of the brain, and that when this organ resumes its activity, the thyroid may probably render up again from its vesicles to the blood, in a still applicable form, those materials which it had previously diverted from their destination.”

Writing a few years later (1849-1852), Handfield-Jones (226) still thought it necessary to adversely criticize the various ancient theories which supposed the thyroid to bear some functional relationship to the larynx. He says that there seems no doubt that the relative position of the thyroid to the larynx is quite unimportant, so far as the function of the organs is concerned. This is borne out by the variations of its site, which occur in birds, and by the results of morbid action, since prodigious goitre does not induce disease of the larynx, except in a mechanical way—*i.e.*, by injurious pressure.

Referring to Simon's theory Handfield-Jones remarks, “It is the only one yet promulgated which can be said to be even probable.” He does not, however, declare himself an adherent to the theory, of which, in fact, he offers several criticisms.

#### K. Extirpation Experiments upon Mammals.

The earliest extirpation experiments upon animals appear to have been performed by Raynard (480) in 1834-1835. This observer reports that the treatment of goitre in dogs can be carried out just as in man. “Il réussit,” says Raynard, “fréquemment pendant l'âge moyen de la vie. Il est fort avantageux pour les animaux âgés. Quant aux jeunes, depuis le sevrage jusqu'à deux ou trois mois, nous avons fait la remarque qu'il est suivi de la mort peu de

jours après, même dès le lendemain de la disparition du goître. Les recherches cadavériques les plus minutieuses ne nous ont fait découvrir jusqu'à ce jour aucune lésion à laquelle on puisse attribuer la mort."

Astley Cooper (92), in 1836, extirpated the thyroid from two pups ten weeks old. Stupidity and malaise supervened, but the animals were killed very soon after the operation.

V. Rapp [quoted by Bopp (54)], in 1840, removed the thyroid from a dog and a goat without ill-effects. But in removing goitre from dogs he found that death ensued soon after the operation.

Bardeleben (17, 18), in 1841 and 1844, could not obtain any ill-effects after removal of the thyroids in dogs and rabbits.

There were other experiments in the same direction published about this period, but most of these were performed under very unsatisfactory conditions, and the results were of little import.

The history of important work on this part of our subject really commences with Schiff, who, during the years 1856, 1857, and 1858 performed at Berne a series of thyroidectomies in various animals. Some rabbits, some rats, some fowls, and some dogs survived the operation, but several dogs, a cat, and a rat died after some days [Schiff (524, 525)]. Schiff explains that, owing to insufficient accommodation, he was compelled to cease his observations after fifteen days.<sup>1</sup>

In 1857, Hegar and Simon (233) removed the thyroid from an old cat, which, a month after the operation, showed no symptoms.

Eléonet (143), in 1866, removed a goitre from a colt without ill-effects.

The work of Schiff remained for many years in complete oblivion. Cretinism had long been recognized, and in 1874 Gull described the condition which Ord, in 1878, called "myxœdema." In 1882 the Swiss surgeons noted the

<sup>1</sup> These earlier results of Schiff were apparently read before the Royal Academy of Science in Copenhagen, and then buried in a work on the formation of sugar in the liver (524).



symptoms of "cachexia strumipriva," or "operative myxœdema," after operations for goitre in man.

After an interval of a quarter of a century Schiff was induced by the observations of Kocher and Reverdin to give renewed attention to the subject. In 1884 he recalled his earlier experiments of 1856-1858, and published the results of a new series of investigations (525). He found that in the rat and the rabbit, thyroidectomy was not followed by any serious result. In the dog and the cat, however, complete removal was fatal. Out of sixty dogs, one survived for fifty days after presenting serious symptoms. Most of the others died during the first week after the operation, though in some cases the fatal result was delayed until the end of the fourth week. Schiff states that the ablation of the thyroid is not fatal if the two lobes were removed in two separate operations, with a sufficient interval between them, an observation which has not been confirmed by subsequent workers. He noted that the symptoms are prevented by a previous graft of a portion of the gland into the peritoneal cavity. "La thyroïdectomie perd ses dangers et une partie essentielle de ses effets, si l'on a introduit et fixé d'abord, dans la cavité abdominale, d'autre corps thyroïde de la même espèce animale."

The symptoms noted by Schiff were general malaise, troubles of locomotion, alterations in sensibility and vasomotor disturbances. He also observed an arrest of growth in a young cat, and in two cases œdema. The chief lesson taught by the experiments of this observer was the excessive danger of complete removal of the thyroid in cats and dogs. This doctrine had a twofold effect. On the one hand it caused surgeons to be very chary in operations on the thyroid, and on the other, it incited experimental physiologists throughout the world to renewed systematic investigations on the effects of thyroidectomy in animals.

Wagner (621), Colzi (89), and Sanquirico and Canalis (515, 516, 517) confirmed Schiff's observations. Horsley (256-263) was the first to operate on monkeys. He states that within about a week after the operation, fibrillary twitches of the muscles of the limbs could be observed. These, like

the similar tremors of paralysis agitans, ceased on voluntary movement. Anæmia and depression supervened, and the animal passed into a "cretinoid" condition. Since monkeys survived the operation for a longer period than did dogs, a myxœdematous condition of the subcutaneous tissues had time to develop. Horsley states that the muscular tremors could be greatly relieved if the animal were kept in a warm room. In his second communication before the Royal Society (262) Horsley states: "In the higher animals—monkeys—the operation on a young individual produces the same result as in a young dog; but, as I showed last year, an older animal, if kept under ordinary circumstances, will survive for six or seven weeks, dying at the end of that time of myxœdema." Horsley describes swellings of the skin of the face, abdomen, etc., due to infiltration of the tissues by mucin. The salivary glands become enormously hypertrophied and the parotid gland, which normally secretes a watery, serous fluid, now takes up a muciparous function and produces quantities of mucin.

These results of Horsley upon monkeys are interesting because some observers both of that period and more recent (*vide infra*) have been unable to verify them. So far as the present writer is aware, Horsley has never given a detailed protocol of his experiments, so that it is impossible to offer any explanation of the difference between his results and those obtained by other investigators.

Extirpation experiments upon animals were also conducted by Welch (627), Albertoni and Tizzoni (4), Fuhr (173, 174), Herzen (238), Rogowitsch (496, 497), and others [Hoffa (250), Ewald (150, 151), v. Eiselberg (142)]. These all supported the view of Schiff as to the effects of total extirpations of the thyroid. But Philipeaux (462), Munk (419, 420), Drobnick (122), and some others, came to quite different conclusions, and so far from admitting the thyroid to be an organ of supreme importance in the economy, attributed the untoward symptoms obtained by other experimenters to injury to nerves, reflex action, and similar causes.

It is worthy of note that experimenters of different periods have recorded a certain number of cases, even in

dogs and cats, in which complete thyroidectomy produced no ill-effects. It is now customary to explain these either by the assumption that the animals had accessory thyroids which had been overlooked, or that the external parathyroids were placed at a somewhat farther distance than usual from the thyroid, and so escaped at the time of operation.

It was, however, soon generally recognized that the Carnivora in most instances died within a few weeks of complete thyroidectomy, and in the majority of cases from acute symptoms, while the Herbivora showed no symptoms, at any rate, for a long time. The difference in the behaviour of the different animals after thyroidectomy was studied in considerable detail by Horsley (256-263). He classified animals according to their susceptibility thus: Birds and rabbits showed no symptoms; the Ungulata—sheep, goat, donkey, pig—showed a general cachexia, with death after a lengthened period; man and the monkey showed a more pronounced train of chronic symptoms, invariably followed by death; the Carnivora, as the dog, cat, and fox, suffered acute symptoms, which were speedily fatal.

The most natural inference was that the marked variations in the susceptibility of different animals corresponded to differences in their metabolism. The flesh-eaters suffered most severely, the vegetable-feeders scarcely at all, while such animals as man and the monkey, who live on a mixed diet, occupied an intermediate position. This supposition was supported by Breisacher (58), who found that dogs fed on meat suffered more severely after thyroidectomy than others fed on milk.

After Gley's rediscovery of the (external) parathyroids (*vide infra*), this observer urged that in the rabbit the fact that previous observers had been able to extirpate the thyroid without ill-effects, was due to anatomical differences between this animal and the Carnivora. In fact, a different operation was performed in the two cases. In the cat and dog the parathyroids, owing to their close contact with the thyroid, were removed along with it, while in the rabbit the parathyroids were placed at some distance away and escaped extirpation. It must be carefully noted

that Gley was referring to the *external* parathyroid. The internal glandule had not yet been discovered. Gley found that when both thyroid and parathyroid were removed, the rabbits usually died within a few days. His explanation was that previous experimenters had removed only the thyroids, leaving the parathyroids behind. The actual fact was, as we now know, that previous workers had removed thyroids and internal parathyroids, leaving the external parathyroids behind, owing to ignorance of their existence.

But Gley did not always induce death by his "thyroid-ectomie complète." Thus, out of fifty-five rabbits operated upon, twelve survived. This would be explained by the majority of modern writers as due to an extra parathyroid, which must have been overlooked at the operation.

Thus Gley taught that the operation of removal of thyroids and parathyroids was practically as fatal in rabbits as in dogs and cats.

The same observer removed the thyroids from dogs, leaving the (external) parathyroids intact, and found that this operation was no more dangerous in those animals than in rabbits. He found, further, that removal of the (external) parathyroids alone produced no symptoms either in dogs or cats. The anatomical information at his disposal did not empower him to attempt the removal of all four parathyroids, leaving the thyroid as intact as possible.

Gley noted also that removal of the thyroid (with the internal parathyroids) in rabbits gave rise to no symptoms, as many previous observers had learnt; but if, at a later period, the external glandules were also removed, the animal died in a few days with acute symptoms. The (external) bodies were then found to have undergone a compensatory hypertrophy and, as Gley believed at this time, more or less of a development into thyroid tissue.

Gley's observations just referred to were published in a series of papers during the years 1891-1897 (184-193), and aroused considerable controversy. Moussu (409) removed both thyroids and parathyroids from nineteen rabbits, and only four died. He extirpated the thyroid from the horse, donkey, ram, and goat, but failed to find the parathyroids. Hofmeister (251, 252, 253) found that removal of the

thyroid only (with, of course, the internal parathyroid) in young rabbits hindered the proper development of the skeleton. Christiani (81, 82) stated that the rat, which had hitherto been placed in the list of unsusceptible animals, succumbed when parathyroids as well as thyroids were removed (see, however, Vincent and Jolly, *infra*).

Gley's results were supported by the observations of Verstraeten and Vanderlinden (607), Cadéac and Guinard (65), Rouxeau (509, 510, 511), Paladino (445). Moussu (409), however, and Blumreich and Jacoby (52), were sceptical. Moussu later (410, 411) and Hofmeister (251, 252) insisted that removal of thyroid only gives rise to a cretinoid condition. As for the development of parathyroid into thyroid tissue, Gley and Nicolas' (199) subsequently became doubtful of this; but these authors remark: "Si l'avenir nous montre que les glandules ne se transforment pas en organes à structure thyroïdienne proprement dite, il ne s'ensuivrait pas nécessairement qu'impuissantes à suppléer la fonction thyroïdienne supprimée, car il n'est pas prouvé que la suppléance physiologique (démontrée dans le cas particulier) doive s'accompagner fatalement d'une suppléance morphologique."

Other papers belonging to this period are referred to under numbers 5, 70, 72, 128-132, 343, 476, 587.

The next important stage in the history of the discussion was reached when Kohn (308, 309) insisted upon the parathyroids being organs *sui generis*, and upon the presence of *two* glandules (an inner and an outer parathyroid) on each side.

Armed with more exact anatomical information, Vassale and Generali made an experimental investigation upon the parathyroids in cats and dogs. In their first paper (597, 598) these authors state that they had, soon after Gley's first communication, in the course of their histological examination of tissues left behind after extirpation of the parathyroids, observed that instead of one, there were in some cases two of these glands on either side. After Kohn's publication in February, 1895, they made themselves well acquainted with the anatomical relations of the four parathyroids, and then proceeded to systematic extirpation experiments. They removed all four parathyroids from

nineteen animals—ten cats and nine dogs—leaving the thyroids intact. Of the ten cats, nine succumbed within ten days, most of them at about the fifth day after the operation, after presenting a typical train of symptoms. These were fibrillary twitchings, muscular spasms, psychical depression, stiff and tottering gait, loss of appetite, tachycardia, rapid emaciation, and lowering of body temperature. One of the cats, operated upon on January 5, 1896, was still alive in March of the same year, but was much emaciated and in a state of chronic cachexia. The nine dogs all died within eight days, mostly on the third or fourth day after the operation. They were as a rule in good health the day after the operation, but began to show symptoms on the second or third day, and then rapidly died, after manifesting a variety of morbid symptoms. These were psychical depression, muscular tremors, paresis of the muscles of mastication, trismus, rigidity of the hind-limbs, uncertain gait, general muscular feebleness, and convulsions. There were also anorexia and vomiting, palpitation and dyspnœa. The urine was scanty and sometimes contained traces of albumin.

The symptoms after removal of the four parathyroids were, as Vassale and Generali pointed out, analogous to those observed after removal of thyroid and parathyroids, an operation which had been so often unwittingly performed since the time of Schiff. The Italian observers did not note very marked convulsions; these only occurred near the fatal termination. The predominating features were, in fact, expressive of diminution of the excitability of the nerve centres; there was, in fact, a rapidly fatal paralysis. The autopsy usually revealed nothing abnormal in the lung; spleen and kidneys were congested. The nervous system was normal with the exception (in some cases) of a certain degree of anæmia.

The authors were satisfied that the fatal issue was not due to complications arising from the operation itself, or to lesions of the thyroid or the surrounding nervous structures. In most cases the wound was in process of healing by first intention; in the cats there was very often complete cicatrization. Vassale and Generali state that the thyroid suffered little or not at all in the operation. In some cases

the thyroid left behind possessed no colloid in its lymphatic spaces. They were surprised to find that death supervened in a shorter time than after removal of both thyroids and parathyroids.

In their second communication (598) Vassale and Generali recorded a series of variations upon their original experiments. Thus they extirpated the two parathyroids of one side, with practically no effects. Removal of the four glands in two operations (first those of one side, then those of the opposite side) showed that the first operation produced little or no result; the second operation proved rapidly fatal. Dogs could be kept in good health with only one parathyroid remaining, but the authors suspected that chronic symptoms might arise at a later period.

In a still later communication (599) the Italian authors state that the tetany induced by thyroidectomy is less marked in old dogs than in young ones. The tetany is particularly well-marked in dogs, if, after removal of the thyroids, they are fed abundantly on a meat diet. If the animals are allowed to get into a condition of hunger, the tetany becomes much less noticeable.

Results similar to those of Vassale and Generali have been obtained by several observers. Early in the year 1897 Rouxau (511), Gley (192, 193), and Moussu (413) published notes of experiments which they thought showed the supreme importance to life of the parathyroids. There seemed, indeed, a certain tendency to under-estimate the functional importance of the thyroid itself. Thus, Gley (193) says: "Il y a lieu de se demander si les troubles consécutifs à la thyroïdectomie ne dépendent pas de la suppression des glandules dites parathyroïdes, au lieu de tenir, comme on le croyait à la suppression de la glande, ou bien si la fonction thyroïdienne appartient à ces deux organes associés." This view is not very different from that which will be urged at a later stage, and received at this earlier date some support from the fact that some observers had failed to notice any ill-effects, especially in rabbits, after removal of the thyroid only, care being taken not to injure the parathyroids. This may be due to one of two causes—(1) the presence of accessory thyroids; (2) the fact that the thyroid is of less functional importance in the adult

than in the young animal. The possibility of the former makes it very difficult to test the truth of the latter ; but Moussu (413) came to the conclusion that for the thyroids and parathyroids there exist two distinct functions : the one, of the thyroid, whose suppression brings on chronic troubles ; the other, of the parathyroid, whose suppression leads to acute symptoms.

Welsh (631, 632) does not consider that there is any very intimate genetic relation between thyroids and parathyroids, or that parathyroid can develop into thyroid. He finds that removal of all four parathyroids in the cat may cause acute and severe symptoms, with a rapidly fatal issue, even though the thyroid be retained practically uninjured.

Capobianco and Mazziotti (73) also report that total parathyroidectomy is always fatal.

Kishi (298) appears to be unaware of the existence of the internal parathyroids in cats and dogs ; at any rate, he makes no mention of the *four* parathyroids which are very regularly present, two on each side, in these animals. This observer, in his experiments on monkeys, only obtained one death out of six, and this with tetanic symptoms.

The present writer, working in conjunction with Professor W. A. Jolly (615), encountered difficulties where, from previous study of the literature, they had not been led to expect them, and the simple and apparently consistent view of the functions of thyroid and parathyroid, which had found favour in recent years, does not seem to them to be borne out by the experimental evidence. This view, briefly stated, is as follows : As regards vital importance, the function of the thyroid is subsidiary to that of the parathyroids. Removal of all the parathyroids from an animal, even if the thyroid be left intact, invariably proves fatal within a short time, and this with typical nervous symptoms described under the name of "tetany." Removal of the thyroid, on the other hand, gives rise to an entirely different train of symptoms, stated to be those of "post-operative myxœdema" or "cachexia strumipriva." According to this modern conception, the history of which has been developed in the preceding pages, the divergent results obtained by the older experimenters in different classes of animals were apparent rather than real, they



having failed to appreciate the anatomical differences, and having, in fact, performed different operations in different classes of animals. This modern theory of the supreme importance of the parathyroids was first clearly put forward by Gley, and has since been elaborated by Vassale and Generali, and other authors.

From the writings of the authors who have supported the modern view, it would appear to be a simple matter to remove, in some cases, the parathyroids, leaving the thyroid intact, and in others the thyroid, leaving the parathyroids *in situ*. Variations of these experiments would appear to be equally simple. Welsh (631, 632), indeed, who worked with the cat, in which parathyroidectomy presents, perhaps, least difficulty, admits some difficulties in performing complete parathyroidectomy. According to Vincent and Jolly, Welsh has understated these. The obstacles in the way of success in this operation are mainly anatomical. The parathyroids are extremely variable in position. The external pair may, as a rule, be easily seen and removed, but the internal are, in the majority of cases, embedded deeply in the substance of the thyroid. When it is remembered how vascular thyroid tissue is, how slightly the parathyroid differs from it in appearance to the naked eye, and how this difference, slight as it is, entirely disappears when there is any bleeding, it will be seen that the operation of digging out the internal parathyroid is one of extreme delicacy. A further difficulty presents itself in the fact that there is a nodule of thymus also embedded in the thyroid lobe, frequently in close proximity to the internal parathyroid, resembling it on naked-eye examination, and therefore easily mistaken for it in the course of the operation. Bearing all these difficulties in mind, the present writer and Professor Jolly did not hesitate to declare that, except in very favourable cases, where the internal parathyroid chances to lie near the surface of the thyroid lobe, the operation is an impossible one. The injury caused to the thyroid in endeavouring to excavate an almost invisible body from its substance, combined with the accompanying profuse hæmorrhage, may account for some of the deaths which other experimenters have attributed to parathyroid insufficiency. It will be obvious that the other operation

—viz., to remove all the thyroid tissue, while leaving the parathyroids with their blood-supply uninjured—is still more difficult, and it was not attempted, though it was found possible in some cases to leave one or two external parathyroids.

The animals upon which the experiments were performed were cats, dogs, foxes, monkeys, rats, guinea-pigs, and rabbits.

Ten out of fifteen cats on which the total operation was performed, either at one or more times, died soon after, the respective periods of survival varying from three to thirty-four days. Five survived the operation. Of the animals which survived, three showed grave nervous symptoms as the result of the operation. The fourth, which was a young cat, ceased for a time to grow, while remaining otherwise perfectly normal. The fifth showed no symptoms. On what theory are we to account for the exceptions to the rule that death rapidly follows the complete operation? These exceptions are fairly numerous, and they have also formed a conspicuous feature of previous investigations. The presence of accessory thyroid or parathyroid tissue suggests itself as a probable explanation, but it must be borne in mind that a careful post-mortem dissection of neck, thorax, and even abdomen, failed to disclose such bodies.

The symptoms usually following the complete operation in the cat are as follows: The cat is perfectly well on the day following the operation; on the second day, there is usually a curious "paw-shaking" and some malaise. This is followed in rapid succession by tremors, stiffness of gait, and convulsions. Even in a quiescent state, the fore-legs tend to be flexed, while the hind-legs are extended, a position exaggerated during convulsions. Hallucinations are fairly common. Of symptoms not directly referable to the nervous system, conjunctivitis and respiratory catarrh were observed.

Two of the cats require a few more words. The first was a youngish cat. On Tuesday, May 10, the thyroid-parathyroid apparatus was removed, except the left external parathyroid. Typical symptoms commenced on the following day, and rapidly became very marked till the animal seemed upon the point of death. After careful nursing,

however, it completely recovered and remained in perfect health till June 13, when a second operation was performed, with the object of removing the remaining parathyroid. This was found to have degenerated. Its fibrous remains were, however, removed. No symptoms ensued. The cat was killed on September 1. The second cat resembled the preceding in exhibiting and recovering from grave nervous and other symptoms. Its health afterwards became perfectly re-established.

Where one thyroid lobe was left and one parathyroid, or two thyroid lobes with one parathyroid, the cats remained perfectly well. Where parathyroids alone were left, out of five cases, only one proved fatal. In this case the animal survived the operation seventy-six days, and died of inter-current disease.

The fact that cats survive where the thyroid gland has been removed, if one or more parathyroids are suffered to remain *in situ*, points to the probability that parathyroid tissue, whether active or not where thyroid tissue is present, can, in its absence, functionally replace it.

Of the experiments upon cats where the thyroid was left and all four parathyroids extirpated, only 33 per cent. proved fatal. One of these had not complete typical symptoms, and it is doubtful whether much weight should be attached to the case. In the other two cases which proved fatal the thyroid gland was found on post-mortem examination to be extensively damaged. *In the great majority of cases no ill-effects of any kind resulted from the operation.* The authors were compelled to conclude from this that simple parathyroidectomy in the cat, where the thyroid gland is left uninjured, is not necessarily fatal. This view is directly opposed to that of Vassale and Generali (*loc. cit.*). Vassale and Generali state that they removed the internal parathyroid with curved scissors. The resulting hæmorrhage must have been considerable. If this hæmorrhage were checked by the cautery much damage to the thyroid tissue must have been caused. Further, the use of curved scissors in this way would necessitate the removal of a large slice of thyroid. The fatal cases in the hands of Vincent and Jolly were those in which they had done most damage to the thyroid. In most of their experiments they picked up

the parathyroid with dissecting forceps, and ligatured it off before excision, thus entirely preventing hæmorrhage.

No myxœdema in cats or cretinism in kittens was observed.

Out of five dogs, the complete operation in one produced no symptoms. So far from exhibiting any morbid symptoms, this dog remained in robust health until attacked by mange, when it was killed, ninety-one days after the operation. There cannot in this case be the slightest doubt that thyroids and parathyroids were completely removed. The operation itself was very satisfactory, and every precaution was taken post mortem to check the result, and no accessory thyroids or parathyroids could be found. The symptoms observed in the dogs which died resembled in many respects those described above as occurring in cats, though on the whole they were less acute; no myxœdematous swellings were observed.

In foxes symptoms appeared within five hours in two cases, and probably in a third, and death soon supervened. In this connection it is significant to note that foxes are the most purely carnivorous of the animals employed. Ligature of the thyroid bloodvessels was not followed by any specific symptoms.

Several previous observers from Schiff (524, 525, 526, 527) onwards had noted the fact that thyroidectomy in dogs and cats is by no means always fatal. At the same time there has been a tendency to disregard the exceptions, and where any explanations have been offered it has been suggested that they are due to parathyroids having been overlooked at the operation, or to the existence of accessory thyroids. Munk (419, 420), indeed, is among the few observers who have laid due stress upon the cases of survival. This observer admits that removal of the thyroid is dangerous, but not that it is an organ essential to life. We cannot assail the logic of the position that the thyroid, which may be frequently removed with impunity, is not "essential to life," and the results obtained by Vincent and Jolly forced them to extend the observation to include the parathyroids also. The observers just mentioned, however, believe that the thyroid has undoubtedly a specific function, which can be performed in its absence by the parathyroids. *Symptoms, when they occur,*

are thus to be attributed to the absence or interference with the functional integrity of both sets of glands. The theory of accessory thyroids or parathyroids is insufficient to account for cases where perfect health is regained after operation, and the conclusion is that the functions of these glands can be otherwise performed, or, indeed, dispensed with. In no carnivore was any condition resembling myxœdema observed.

In monkeys no symptoms of myxœdema were observed when thyroids and parathyroids were completely removed. These results differ from those obtained by Horsley, Murray, and Edmunds (*loc. cit.*), who state that it is possible by operation to induce myxœdema in monkeys. The animals were kept at ordinary indoor summer temperature without any steps being taken to raise it artificially, yet there were no symptoms which could be described as myxœdematous. This corresponds with the observations of Munk (*loc. cit.*) and Kishi (*loc. cit.*). Kishi, however, as we have seen, obtained one death out of six with tetanic symptoms. The animals were occasionally subject to catarrh, and one died of some laryngeal affection, and it seems probable that, as in the case of other animals, removal of the thyroid gland leaves monkeys in a condition in which they are less capable of resisting disease.<sup>1</sup>

A very interesting result of the experiments is that the removal of the parathyroid glands, included, of course, in the complete operation, never proves fatal, although in some cases transient nervous symptoms were observed. There is no reason to attribute death which occurred in two cases to absence of thyroids or parathyroids, since the death-rate of unoperated monkeys kept in a laboratory is frequently high. It would appear that the parathyroids do not possess in monkeys so important functions as in the Carnivora. In monkeys neither the thyroids nor parathyroids are essential to life.

<sup>1</sup> Fjeldstad (160) has recently reported that removal of the thyroids from the rabbit does not, at least, during the first month, appreciably affect the formation of immune bodies (more specifically the agglutinins). It is therefore probable that any increased susceptibility to infection in such animals must be ascribed to causes other than the depression of the immunity reaction.

Carlson and Jacobson (75) find that the livers of completely thyroidectomized rats and foxes that exhibit typical symptoms of intoxication show a marked depression of the ammonia-destroying power as compared to the liver of normal animals.

In rats there appears to be only one parathyroid in each thyroid lobe. Thyroids and parathyroids may be destroyed or removed without affecting the animal in any way.

In guinea-pigs similar results were obtained, but in rabbits the matter is doubtful.

Thus, *in a series of experiments upon cats, dogs, foxes, monkeys, rats, and guinea-pigs, more than 51 per cent. survived the operation for a prolonged period, and of these more than 68 per cent. showed no specific symptoms of any kind.* In making these calculations rabbits were left altogether out of account. *There is a fundamental difference of behaviour, as Horsley taught, between different classes of animals, and this is as true when the parathyroids enter into the discussion as when omitted.* It is not therefore due to anatomical difference, nor probably to mere variations in feeding, but to deep-seated physiological conditions.

The authors' conclusions were as follows: "It cannot be truly said that either thyroids or parathyroids are essential for life, since it is frequently possible to remove either or both without causing death. Rats and guinea-pigs do not seem to suffer at all as the result of extirpation. Monkeys only show transient nervous symptoms. Dogs and cats frequently, but by no means invariably, suffer severely, and die. In foxes, symptoms come on with very remarkable rapidity, and death is correspondingly early.<sup>1</sup> The diversity of results obtained in different classes of animals is not to be attributed to anatomical, but to physiological differences. In no animals have we been able to induce symptoms resembling those of myxœdema. In young animals, although extirpation of the thyroid causes a temporary cessation of growth, we find that this is not necessarily accompanied by symptoms of a cretinoid nature. Myxœdema and cretinism must then, we think, be due to causes more complex than simple thyroid insufficiency. When the thyroid is removed the parathyroids appear capable of functionally replacing it to a certain extent, and their histological structure changes accordingly."

In their second communication (616), Vincent and Jolly report the results of a further series of experiments upon monkeys, cats, dogs, prairie-wolves, badgers, and rats.

<sup>1</sup> See, however, Carlson and Woelfel (77).

The experiments on monkeys, six in number, confirm those previously recorded. There were transient nervous symptoms in two cases, but the monkeys entirely recovered from them. The authors were inclined to think that the acute nervous symptoms are frequently associated with damage to the nerves at the operation. In none of the monkeys were there any of the signs observed which are described as most characteristic of myxœdema in the human subject. Never were there any swellings of the skin or subcutaneous tissue in any part of the body, nor were such swellings induced by the transfer of two monkeys from the warm to the cold room, although one of them died as a result of the altered conditions. With the exception of the nervous symptoms, from which recovery was the rule, the monkeys exhibited no very definite ill-effects as the result of the operation. The monkeys were shown to other workers in the laboratory, and were exhibited at meetings of societies, but neither the authors nor any of those who saw them could diagnose myxœdema. The absence of myxœdematous swellings in both series of experiments—that is to say, after thirteen complete extirpations in monkeys—is in accordance with the results of Munk (*loc. cit.*) and Kishi (*loc. cit.*).

The experiments on cats gave results which confirmed those previously reported.

An attempt was made to test the effect of removal of all the parathyroids in dogs, leaving the thyroid as little damaged as possible. The results supported the view that in extirpation experiments symptoms, when they occur, are to be attributed to interference with the functional integrity of both thyroids and parathyroids taken as a whole. If one removes the parathyroids, and does little or no damage to the thyroid, the animal appears to suffer no ill consequences, or if one removes a considerable portion of the thyroid, and yet leaves the parathyroids, a similar negative result will follow. But if the parathyroids be removed, and considerable damage be done to the thyroid, or if the thyroid lobes be removed and the parathyroids injured, we may frequently get acute symptoms and rapid death. But it must be remembered that this is not a constant rule, for in many cases with various groups of mammals we can remove the

whole apparatus with impunity. Especially is this the case with rats.

The wolves behaved after extirpation of their thyroids and parathyroids precisely as do dogs, and badgers and rats were totally unaffected. The authors' conclusions were as follows :

“Neither thyroid nor parathyroids can be considered as organs absolutely essential for life. Rats and guinea-pigs do not seem to suffer at all as the result of extirpation. Monkeys only show transient nervous symptoms. Dogs, cats, foxes, and prairie-wolves frequently suffer severely and die. On the other hand, badgers do not appear to be affected by the operation. When parathyroidectomy proves fatal, this is probably due to the severe damage simultaneously done to the thyroid, and it is possible that there may be a difference between the results of severe damage to the thyroid apparatus and its total removal. Thyroid and parathyroids are to be looked upon as a single physiological apparatus, the two kinds of tissue being intimately associated embryologically, and working together physiologically. When the thyroid is removed, the parathyroids appear capable of functionally replacing it to a certain extent, and their histological structure changes accordingly. In no animals, not even in monkeys, have we been able to induce any swellings of the subcutaneous tissue, which is the striking feature of myxœdema in the human subject. We think, therefore, that the pathology of myxœdema must be more complex than simple thyroid insufficiency.”

Forsyth (164) quotes the results of Edmunds as illustrating the contradictory nature of the operative effects, and as regards the extreme difficulties of the operation of parathyroidectomy is in entire accord with Vincent and Jolly. He points out, as did the last-named observers, that parathyroid glands often possess no naked-eye characteristic sufficient to insure identification. They do not possess that constancy of position with which they have been credited. They are not constant in number. They may be associated with lymphatic glands, thymic residues, or accessory thyroids. They may be deeply buried in the thyroid. Both in the thyroid and on its surface they may be microscopical in size. In face of these considerations Forsyth considers



that we are not justified in concluding that the parathyroid glands have been proved to possess a function of such vital importance that their suppression leads to rapid death. Forsyth, as will be seen more fully later, believes that the parathyroids are portions of the main thyroid gland which have assumed functional activity, but have not yet formed vesicles.

Pepere (454-458) upholds the theory of a separate and important function for the parathyroids, and lays great stress upon the constant occurrence of accessory parathyroids as explaining the numerous cases where parathyroidectomy produces no symptoms.

MacCallum (346, 347, 348) is very dogmatic upon this point. He states: "At least we know well that the destruction of all the parathyroid glands results in the death of the animal with symptoms of tetany, which is not in the least dependent, as was once taught, upon the destruction of the thyroid gland." He further states that his own experiments have convinced him "beyond doubt or question" as to the correctness of the observations. It must be submitted that in the present state of our knowledge such expressions are premature and unwarrantable. It will be admitted from a perusal of many parts of the present work that at any rate there is much to be said on the other side.

- MacCallum and Voegtlin (351) have recently attempted to utilize the theory of a separate and supreme function of the parathyroids to explain the pathogeny of different forms of "tetany" which occur in clinical observations. There have now been very numerous attempts to connect lesions of the parathyroids with various diseases of a tetanoid nature.<sup>1</sup> There will not be space to deal with this part of the subject very fully. A paper by Yanase (649) will illustrate the nature of these attempts. This author finds hæmorrhages in the parathyroids in cases in which there was increased sensitiveness to the galvanic current, and suggests a connection between this and tetany.

MacCallum and Voegtlin state that the effect of the extirpation of the parathyroid glands may be annulled by the re-introduction of an extract of these glands even from an animal of widely different character. The active principle is

<sup>1</sup> See Grosser and Betke (205).

associated with a nucleo-protein in the extract, and may be separated along with this nucleo-protein from the remaining inert albuminous substances. Its effects in counteracting tetany appear some hours after injection, and last several days. According to these authors, tetany may be regarded as an expression of hyperexcitability of the nerve cells due to deficiency of calcium salts. Berkeley and Beebe (35) confirmed these results, and in addition found that salts of the chemically closely allied substance, strontium, had a similar and equally pronounced effect. Biedl (39) reports similar results, but he does not find that these salts prolong the life, despite the suppression of the excitation symptoms. Haberfeld (212), Haskins and Gerstenberger (230), and others have attempted to bring all types of clinical tetany within the category of parathyroid tetany.<sup>1</sup>

Quest (477, 478) believes that the origin of tetany is intimately related to the calcium metabolism. Pexa (460) is of a contrary opinion.<sup>2</sup>

Carlson and Jacobson (75), as already pointed out (p. 300, footnote) find that the livers of completely thyroidectomized cats and foxes that exhibit typical symptoms of intoxication show a marked depression of the ammonia-destroying power as compared with the livers of normal animals. So there is increased blood ammonia in animals in parathyroid tetany. Clara Jacobson (283) believes that this increased ammonia is directly responsible for the tetany.

In a later paper Carlson and Jacobson (76) seem to abandon this view, and put forward the theory that, with the exception of parathyroid transplantation, the action of all measures which suppress the excitation symptoms can be accounted for by *decreased excitability*, primarily, of the nervous tissues. The excitability is decreased *directly* by the drug action of the calcium and strontium salts, and by hypertonicity; indirectly by substances or measures which cause partial anæmia of the brain through vasodilation (tissue extracts, albumoses, amyl nitrite, stimulation of the depressor nerves). None of these measures have, therefore,

<sup>1</sup> See Jörgensen (235, 236), Jovane and Vaglio (292), Roussy et Clunet (508), Wiener (640), Wirth (643), Iversen (281, 282), Auerbach (13), Alquier (6).

<sup>2</sup> On the subject of the calcium metabolism in tetany, see also Schabad (522), Neurath (427), Rosenstern (504), Arthus u. Schafermann (10).

any *specific* significance as regards the cause and nature of parathyroid tetany.

It has been found that other salts than those of calcium and strontium are of some temporary benefit in experimental tetany. Thus, Joseph and Meltzer (290) report that sodium chloride has an inhibitory action. Magnesium, according to Canestro (67), and thorium and lanthanum, according to Frouin (170), have a similar effect.

A very instructive series of experiments has recently been reported by MacCallum, Thomson, and Murphy (350). These observers described the anatomy of the parathyroids in sheep and goats as above referred to (p. 255), and removed the parathyroids from both the thyroid and the thymus. From these experiments they admit that there is indeed a very marked difference between the results obtained by parathyroidectomy in the dog, and those in such animals as the sheep and goat. Practically no effect whatever was produced in five sheep, although in at least three of them ample time elapsed for the development of symptoms. In eight goats there was fairly definite twitching without actual tetanic convulsions in four; two showed no symptoms at any time; while two developed perfectly typical and extremely violent tetany, leading at least in one case to the death of the animal.

There can be no doubt that the results of extirpation of thyroid and parathyroids are indeed very different in different classes of animals, and this altogether independently of any anatomical considerations. This is especially noticeable between, for example, dogs and monkeys. When thyroid (and parathyroids) are removed from dogs, the animals frequently die with acute symptoms within a short period. When the same operation is performed on monkeys, they most frequently live for several months without any very noticeable effect.

MacCallum, Thomson, and Murphy do not know how to explain satisfactorily the negative results in so many of their animals, unless it be that, in spite of their extremely careful and conscientious search, there were still other masses of parathyroid tissue hidden away somewhere in the neck or thorax. It is important to recall that Vincent and Jolly (615), and Halpenny (217) obtained very indefinite results

with rabbits, though the latter observed tetany in a few animals. The insistence upon the necessary presence of remaining parathyroids somewhere or other in all cases where symptoms did not occur, in investigations made to discover whether or not parathyroids are essential to health, is a distinct case of reasoning in a circle. And, further, if accessory glands be so usually present, then the question as to the importance of the glands ceases to have the value hitherto attached to it.<sup>1</sup>

Morel (406) believes that the fundamental cause of tetany after parathyroidectomy is an "acidosis." The same author (407) records the suppression, as a result of injuries to bones, of the parathyroid tetany. Gley (198), in referring to this and other observations of Morel, recalls some of his earlier experiments, showing that after parathyroidectomy one may sometimes observe symptoms usually attributed to simple thyroidectomy (cachexia). Professor Gley puts these facts forward once more in support of his theory of a functional relationship between thyroids and parathyroids, a theory supported from many different standpoints throughout the present work.

Halsted (222) uses the term "tetania parathyreopriva," and describes "plumpness" and loss of hair in a dog as myxœdema, "although the spirits and general health are good." Although this author presumably believes in a totally separate and distinct function for thyroid and parathyroid, and believes further that parathyroidectomy is fatal, yet he records some observations which tend to prove quite the contrary. He does not, it is true, lay much stress on these observations, nor does he appear to appreciate their significance. On p. 179 he says: "Dog has not been at all well since the operation. Believed to be suffering from parathyroid privation due to considerable insult to both thyroid glands, as well as to the excision of two transplanted bodies." Again, on the same page we read: "The experiment is cited to show what I observed very frequently in my experiments . . . that mere handling of the thyroid lobes may give rise to symptoms of parathyroid privation.

<sup>1</sup> Rossi (504) obtains variable results in sheep. Sometimes complete parathyroidectomy gives rise to fatal convulsions, at other times the operation is well tolerated.

Manipulation, not excessive, of the thyroid gland in dogs has several times in my experience produced fatal tetany." This is, indeed, a very severe criticism of the interpretation of Vassale and Generali, and of other authors who support the " vitally essential " theory of the parathyroids, and lends strong support to the view urged by Vincent and Jolly, and by Forsyth, that thyroid and parathyroid are to be looked upon as one apparatus. One is tempted to inquire what conclusions can possibly be drawn from parathyroidectomy if damage to the thyroid may produce the same symptoms.

In further reference to the experiments upon monkeys performed by Vincent and Jolly, it has been objected that the animals were not kept for a sufficiently long time, and that myxœdema might have developed had they been under observation some weeks or months longer. The reply to this criticism is that the monkeys were kept under observation for a period far beyond that within which myxœdema is reported to have been noted by Horsley and other observers.

Halpenny and Gunn (219), in repeating the extirpation experiments upon monkeys, report that the operation was much more serious in their hands than in those of Vincent and Jolly, though, except in one doubtful case, there was no sign of myxœdema. Carlson and Woelfel (77) report that myxœdema does not develop in thyroidectomized rabbits at least in seven months, nor in the monkey in several months.

The symptoms observed (perhaps most typically in dogs) after thyro-parathyroidectomy have never received such detailed attention as they deserve. The majority of modern writers have been content with referring to " cachexia," on the one hand, and " tetany " on the other, without taking pains to enter upon any detailed analysis. Some features of the syndroma have been emphasized by Carlson and Jacobson (76). One of the most remarkable of these is the periodicity of the attacks. After violent attacks lasting sometimes for several hours, the dog will completely recover, and might pass for a normal animal, eating and drinking and playing about as usual, though for a certain period after each attack some depression may be noted. According to Carlson and Jacobson, the duration of this spontaneous recovery varies from a few hours to thirty-six hours. This corresponds fairly well with the experience of the present

writer, though the periods cannot be stated with any degree of certainty unless the animals are watched continuously day and night. As remarked by the above-mentioned observers, it is obvious that this spontaneous periodicity is a disturbing factor in the study of therapeutic measures which have at best only a temporary action.

The variability in the symptoms has been observed, not only between different series of experiments by different observers, but in individual animals of a particular series. Sometimes symptoms of depression preponderate, sometimes those of excitation. Again, the rapidity of onset of the symptoms, their degree of violence, and the duration of life, vary within the widest possible limits.

Anorexia sometimes occurs, but as a rule the animals eat well between the attacks. Vomiting is frequent, and may give rise to convulsions. Diarrhœa, with offensive stools, is very characteristic.

The increased reflex excitability may cause moderate stimuli to produce convulsions. In some cases in the later stages the excitement of being stroked, or even of drinking, may bring on an attack.

Perhaps the most striking of all the symptoms is the occurrence of paroxysms of rapid breathing. This has been noticed by previous observers from Schiff on, but not much emphasis has been laid upon it. Schiff called the phenomenon "cardiac respiration," and attributed it to stimulation of the phrenic nerves by the currents of action of the heart during contraction. This is to be regarded as an example of an increased excitability of the motor nerves. The gasps are synchronous with the heart-beats and very loud, so that they can frequently be heard in distant parts of the laboratory.

Decreased sensory excitability appears to be present in the later stages.

#### L. Experimental Pathological Anatomy.

##### *Changes observed Post Mortem in Animals after Extirpation of Thyroids and Parathyroids.*

The changes after simple thyroidectomy have not been very thoroughly studied, owing, no doubt, to the extreme difficulty of the operation; but it is supposed that the

changes in the skeleton found after extirpation of thyroids and some of the parathyroids are due to lack of thyroid. The same may very possibly apply to the changes found in the genital organs [Hofmeister (253)].

After removal of thyroids and parathyroids together chronic symptoms may arise, and numerous alterations in different organs and tissues have been described. In the nervous system anæmia and œdema of the brain [Sanquirico and Canalis (515), Fuhr (173)], destruction of nerve cells [Albertoni and Tizzoni, (4)], hæmorrhages and degeneration in the crossed pyramidal tract and column of Goll, and changes in peripheral nerves [Lupo (343), Loewenthal (338)]. Rogowitch (497) describes a subacute parenchymatous encephalomyelitis. (See, however, Tizzoni and Centanni (578), Marinesco (367), Vassale (593). The evidence as to changes in the nervous system is conflicting. For other contributions to this subject, see Capobianco (71), Pisenti (464), de Quervain (476), Rosenblatt (503), Masetti (366), Katzenstein (295), and Lusena (344).

Congestion, hæmorrhages, and fatty degeneration of the liver [Sanquirico and Canalis (515), Rogowitch (498), Quinquaud (479), and others], and changes in the kidneys, have been recorded [Laulanié (324), etc.]. In the stomach and intestines congestion and excoriation of the mucous membranes have been described [Sciolla (542), Lusena (345)]. The statements as to the salivary glands are contradictory, and the same applies to the spleen, adrenals, and other organs. As for the lungs, broncho-pneumonia, congestion, splenization, and emphysema are among the conditions recorded [Arthaud and Magon (9), and others]. Under the head of the vascular system, changes in the wall of the blood-vessels, thickening, and atheroma have been described [Moussu (412), Rosenblatt (503), v. Eiselsberg (142)]. In the blood itself there is usually hyperleucocytosis and a diminution in the red corpuscles [Horsley (259), Pokrovsky (468), Mezincescu (394)], while it is stated that there is an increase of carbon dioxide, and that the fluid becomes toxic [Ricou and Hofrichter (489), Colzi (89)].

The thymus appears to atrophy, as in many cases of malnutrition. Changes in the pituitary body have been already referred to. In the ovaries Hofmeister (251) describes a

premature maturation, and in some cases an atrophy of the follicles. The same author also records a certain degree of atrophy of the testes.

The cartilages in young animals remain unossified,<sup>1</sup> and there is a diminution of the normal cellular proliferation, swelling, and the formation of clefts in the ground substance, and atrophy of the cartilage cells [Hofmeister (251), Jandelize (284)].

The alterations after extirpation of all four parathyroids, leaving the thyroids uninjured, have been studied in the dog by Vassale and Donaggio (294, 295), and by Vassale and Friedmann (296). These observers found degeneration in the crossed pyramidal tracts and the posterior columns. But, as stated on a previous page, these observations have not been confirmed by all subsequent workers.

The subject has been recently reinvestigated by Halpenny (217), who finds it impossible to confirm the statement that complete parathyroidectomy invariably proves fatal. Again, he has not been able to confirm a very generally accepted statement that parathyroidectomy alone is a more rapidly fatal operation than thyro-parathyroidectomy. In his experiments death has occurred earlier, on the average, with the complete operation than with parathyroidectomy. Halpenny could not find any signs of degeneration in the spinal cord of animals which died after parathyroidectomy, such as was described by Vassale and Donaggio (294, 295). (This point was investigated for the present writer some years ago in Edinburgh by Dr. Sutherland Simpson, with similarly negative results.) No myxœdematous swellings could be detected in any of the animals.

### M. Chemistry of Thyroids and Parathyroids.

#### *The Relation of Iodine to the Structure and Functions of the Thyroid Apparatus.*

The question naturally arises, What is the chemical nature of the active principle of the thyroid gland? What is the substance, or what are the substances, manufactured by the thyroid and supplied to the body, the absence of which causes such serious metabolic disturbances in many animals,

<sup>1</sup> See also Erdheim (147) and Togofuku (580).



and the supply of which, in the form of a graft or subcutaneous or stomachic administration, obviates or relieves such disturbances? We may say at once that there is at present no satisfactory answer to these questions. The "active principle" of the gland is unknown, and there are no direct pharmacological or chemical means of testing the value of thyroid preparations, apart from actual clinical trial.

In 1895 Baumann (20, 21, 22) discovered the presence of iodine in the thyroid gland, and prepared a substance from it, containing as much as 9.3 per cent. of iodine. This is an organic compound of iodine, and is prepared by treating thyroids with 10 per cent.  $H_2SO_4$  with the aid of heat. On cooling, a precipitate comes down, which is dissolved in alcohol. From the alcoholic residue the fat is dissolved in 10 per cent. caustic soda. The brown solution is precipitated again with sulphuric acid. The product is a brown amorphous substance, insoluble in water, and soluble with difficulty in alcohol. It is readily soluble in dilute alkalis, and is precipitated by acids. It contains no protein, but some phosphorus (0.4 to 0.5 per cent.). (The amount of iodine per gramme of the organ in human adults varies from 0.3 to 0.9 per cent.). This substance has been put upon the market under the name of "thyroidin" by Bayer and Co., of Elberfeld.

Baumann and Roos (25) considered it certain that the iodine is an important part of the "active principle" of the thyroid. They claimed, in fact, that Baumann's "thyroidin" was the active principle of the gland. They based this view upon the physiological action of the substance in health and disease, and on the fact that iodine is so generally found in the thyroid in health, and is absent or diminished in amount in certain forms of goitre.

Hildebrandt (242) found that thyroidin alone is able to counteract the effects of thyroidectomy and to keep an animal alive. It represents, according to him, the physiologically active principle of the thyroid gland. This author states that the excretion of albumin and sugar in the urine which accompanies the severe symptoms induced by thyroidectomy ceases under the administration of thyroidin. Other salts of iodine are unable to prevent the onset of

symptoms, or to relieve them after they have appeared. As to the fate of the iodine of the thyrioidin, he finds that it is held back in the body with extreme ease, while simple iodine preparations appear almost at once in the urine. He lays special stress on the fact that thyrioidin does not appear in the urine of a dog from whom the thyroid has been removed; hence other organs of the body must have the power of holding back the thyrioidin. On the other hand, the building up of the complicated combination present in thyrioidin from the simple iodine is to be looked upon as a specific function of the thyroid gland. Blumreich and Jacoby (52) express a similar opinion: "Die Wirkung der Schilddrüse besteht wahrscheinlich in der ueberführung einer giftigen in eine ungiftige Sustanz; durchaus möglich ist, dass es sich dabei um eine Umwandlung von Jod in Thyrioidin handelt, das dann weitere Wirkungen im Organismus entfalten kann." Baumann (20) noted a rise of the iodine present in the thyroids of animals treated with potassium iodide or iodoform.

Vassale (591) held that intravenous injection of thyroid extract could prevent the ill-effects of thyriodectomy. Thuneberg (577) obtained contrary results. Baumann and Roos (24), Baumann and Goldmann (23), and Hofmeister (254), agree that thyrioidin is able to supply the function of the gland after removal. But Gottlieb (201) and Notkin (431) are of the opposite opinion. Wormser (648) believes that none of the single substances obtained from the thyroid is able to replace its function, and thinks that it is necessary to give them all at the same time if they are to serve as substitutes for the normal internal secretion of the gland.

Stabel (556, 557), at about the same time, came to the conclusion that neither thyrioidin nor thyroid gland substance were able to keep dogs alive after thyriodectomy. So also Pugliese (474). This observer removed the thyroids from twelve dogs, and fed the animals on thyroid "tabloids." All the animals died at 2, 3, 6, 7, 12, 16, 23, 30, and 68 days after the operation, the earlier ones from tetanic symptoms, the later ones from cachexia. Pugliese's observations, then, stand in opposition to those of Gottlieb and Wormser, but in agreement with those of Stabel, and show that the giving of thyroid preparations is in no way able to keep an animal

alive after thyroidectomy. It is thus evident that Baumann's thesis as to the identity of his thyriodin with the actual functionally active principle of the gland has not been sustained by all later observation. At any rate, the statements on this point are very conflicting. Coronedi (93) has reported that the administration of haloid fats has a marked effect in preventing the onset of symptoms after thyroidectomy in dogs and rabbits, and this result points to the therapeutic value of organically combined iodine.

But there are many objections to Baumann's theory. Iodine is not invariably present in the thyroid gland. Baumann himself states (22) that, while the thyroid of a dog fed upon Spratt's dog biscuits contains iodine, this element is absent after a meat diet. In the ox, horse, and pig, iodine may be absent, or may be present in the merest traces [Töpfer (579)]. Further, Baumann states that iodine cannot always be found in the human thyroid. Thus it is frequently absent from the thyroids of children.

Miwa and Stoeltzner (401) and Neumeister (426) have fully confirmed these observations and emphasized the dependence of the iodine content of the thyroid upon the diet. These authors argued that the iodine usually found in the thyroid has no more significance than the traces of copper so often found in the liver. Roos (502) found no iodine in the thyroids of three foxes; none in that of a polecat; none in that of a wild cat; he found it in but two of six martens; it was absent from the thyroids of four domestic cats, and present in but traces in five others; in dogs it was absent in four out of eleven, in two out of four horses, and three out of seven pigs. The presence or absence of iodine seems to depend in many cases on the character of the animal's food. According to Roos, the thyroids of herbivorous animals, whose food usually contains small amounts of iodine, are richer in this element than those of carnivorous animals, whose food is usually poor in iodine. Suiffet (567) states that sheep pastured near the sea may have double the amount of iodine in their thyroid as those pastured in inland regions. The amount of iodine in the thyroid of omnivorous animals (hog, dog, man) is exceedingly variable. Nagel and Roos (423) report variations in the amount of iodine under various conditions. Baumann (22) found the

percentage of iodine in the thyroid of horses to vary from 0.06 to 0.17.

Now, the animals whose thyroids contain no iodine appear to be as healthy as those whose glands contain an abundance of this element, and removal of the gland is followed by just as severe symptoms in the former as in the latter. In many instances, indeed, the animal whose thyroid contains no iodine (such as a dog fed upon a meat diet) will exhibit very pronounced symptoms after thyroidectomy, while sheep (whose thyroids usually contain considerable amounts of iodine) will probably show no symptoms as a result of the operation [see MacCallum, and others (350)]; so that a thyroid gland free from iodine seems to meet the needs of the body as well as the thyroid that contains iodine. It is clear, indeed, from the extirpation results just alluded to, that some of the important, if not the most important, functions of the gland are independent of its iodine content.

Jolin (288) finds great variations in the iodine content of the human thyroid, and is unable to discover any relation between its amount and conditions of health. He suggests that iodine is an accidental constituent of the thyroid, or that among the functions of the gland is that of taking up an excess of iodine in the blood and storing it. Similar views have been expressed by Bunge (63), Meltzer (387), and Abderhalden (1).

Reid Hunt and Seidell (273) suggest an intermediate view—viz., that thyroid free of iodine may have a certain degree of activity, although this is much less than that of thyroid-containing iodine.

One of Baumann's chief arguments in favour of his view that thyroiodin is the active principle of the gland, lay in the observation that administration of thyroiodin in cases of goitre causes disappearance of the tumour. But this is a known remedial action of iodine, *qua* iodine [Coindet (88)], and proves nothing as to the therapeutic efficiency of the thyroid preparation. Good results have been obtained by the administration of various inorganic and organic preparations of iodine [Schöndorff (533)], and certain sea animals and plants which contain iodine have been used as medicaments, and especially in cases of goitre, for hundreds of years before the discovery of iodine [Bunge (63), Harnack

(228), Monéry (403), Kocher (302)]. It is possible, as Bunge (63) suggests, that the organic form of iodine may be more readily absorbed, and reach the part where its influence is effective.

Thymus has been found by some observers to have an effect upon goitre similar to that of thyroid [Mikulicz (396), Reinback (482), Cunningham (105)]. But the thymus contains little or no iodine [Baumann (21), Cunningham (105), Wells (628), Mendel (290)], and Hunt (272) has shown that there is present in several organs of the body a substance or substances having a physiological action similar, at least in some respects, to that of thyroid, but that the latter, apparently on account of its iodine content, is far more active.

Hutchinson (276) prepared an artificial iodized nucleo-albumin by extracting the thymus of calves with dilute alkali, and obtained a product which contained 4 to 7 per cent. of iodine. This had no effect in warding off the symptoms after thyroidectomy in dogs. These results agree with those of Hellin (236), who also found iodized albumin and nucleo-albumin, prepared from the spleen, to be inactive. Blum, who at first (50) asserted that his iodized albumin produced the same effects in myxœdema as the thyroid, has in his more recent papers changed his view (51). "It seems probable, indeed," says Hutchinson (276), "that these compounds possess no advantage as pharmacological agents over the iodide of starch which has so long been known and administered."

Hutchinson also prepared some artificially iodized colloid containing 3.23 per cent. of iodine, and succeeded in making the protein-free body take up a large additional quantity of iodine. The pharmacological effects of the fortified products were not found to be greater than those of the originals. Hutchinson concluded from the whole evidence that the iodine in the thyroid gland, if it plays an essential part in the activity of the latter at all, does so simply in virtue of the special form of combination in which it is present.

Roos (502) fed a series of dogs with iodine until the iodine content of the thyroid had been considerably increased, and found that such thyroids showed increased physiological activity.

Reid Hunt and Seidell (273) have recently reported that there is a close parallelism between the iodine content of the thyroid and its physiological activity as measured by its effects in diminishing the resistance of rats to acetonitrile, and of rats and mice to morphia. Olds (434), however, has recently reported that thyroidectomized rats show the same resistance to morphine-poisoning as normal rats, at least within a period of eight to twenty-eight days after the operation. This fact seems to question, or at least limit, the Hunt test for the concentration of thyroid secretion in the body fluids. Hunt and Seidell describe experiments which tend to show that, where potassium iodide or iodoform is administered to dogs, the thyroids of the latter contain a greatly increased percentage of iodine, and are also much more active physiologically. They conclude that thyroid rich in iodine is more active than thyroid poor in iodine, and that the iodine is the cause of the activity.

Within the last two years renewed attention has been given to the methods of determination of iodine and its estimation in the thyroid gland. Hunter (274) has modified Baumann's (25) method. The object of the new method is the complete transformation of the iodine to the *iodic* state, and the final measurement is titrimetric. Several advantages are claimed for this method, which has been adopted by Seidell (543) in some new experiments upon the determination of iodine in thyroid. This author finds that in a series of seven dogs the percentage of iodine in the thyroids varied from 0.036 to 0.271. The causes for this wide variation are diet, age, breed, etc. According to Simpson and Hunter (554), the fresh weights of the thyroids of ten sheep varied from 1.6 to 24.7 grammes, and the percentage of iodine in the dried samples from 0.048 to 0.383—a somewhat wider variation than was found by Seidell in dogs.

Marine and Lenhart (361) have investigated the relation of iodine to the structure of human thyroids. They conclude that iodine is necessary for normal thyroid activity. The iodine content in goitrous glands varies inversely with the degree of hyperplasia. The percentage of iodine present in thyroids is variable, but there is a quite constant minimum percentage necessary for the maintenance of normal or

colloid gland structure. Exophthalmic goitre is constantly accompanied during the progressive stage of the disease with thyroid hyperplasia, and the iodine percentage varies inversely with the degree of hyperplasia. In endemic cretinism and in myxœdema the fibrous overgrowth, with atrophy of the gland cells, is consequent on active hyperplasia, and is associated with a very low iodine content.

Oswald (442) in 1899 considered the iodine of the thyroid gland to be bound up in a globulin-like body, and the compound was called by him "thyreoglobulin." This, he said, has all the physiological properties of "thyroidin" [Cyon and Oswald (112)]. From it one can isolate the thyroidin. The thyreoglobulin forms, along with a nucleoprotein, the colloid substance of the thyroid vesicles. In 1910 the same author (443) reports that iodine is split off in ionized form by the breakdown of the protein molecule of the thyroid. One part of the protein molecule is easily destroyed, setting free iodine, even by simply heating with acids or alkalies, or by the action of trypsin for a short time. Another part is destroyed with much greater difficulty, only after the action of trypsin and erepsin for months. Through the autolysis and decomposition with the breaking off of iodine from its organic combination, the specific physiological action of "iodo-thyreoglobulin" is lost. Strong ferments destroy artificially iodized protein in such a way that the iodine is ionized.

Notwithstanding all the painstaking investigations which have been carried out upon the chemistry of the thyroid gland, no chemically pure substance has yet been isolated, and the presence of the iodine is still of problematic significance. It has been stated, as we have seen, that iodine is not always present in the thyroid gland, and that animals whose thyroids are devoid of iodine do not manifest any signs of ill-health. It is also alleged that organically combined iodine, whether in the form of thyroid substance or in any other combination, may be used with good results in diseases of the thyroid. The facts that the thyroid has the power to store up iodine from the food, and that glands with a rich supply of iodine are more beneficial as medicaments than those poor in iodine, can scarcely be without

some significance. It may be that animals whose thyroids contain no iodine are not in reality in perfect health, and that careful investigation would show that they are more liable to infection than others.<sup>1</sup>

A question of considerable interest is the occurrence or non-occurrence of iodine in other glands and tissues of the body. Thus, there appears to be no iodine in the pituitary body [Schnitzler (532), Wells (629, 630), and Denis (117)]. Of special importance, in view of the discussion (*vide infra*, p. 337) as to the relationship between thyroid and parathyroid, is the question as to the occurrence of iodine in the parathyroids. Gley (191) found iodine in the parathyroids in larger amount than in the thyroid. The presence of iodine in the parathyroid has been confirmed by Mendel (390) and by Pagel [cited by Jeandelize (284)]. But Estes and Cecil (149) state that the iodine content of the parathyroid gland is insignificant. The matter obviously requires reinvestigation. The parathyroid frequently contains colloid vesicles in some regions, and it seems likely that in such cases an appreciable amount of iodine would be detected, at any rate, in those animals whose thyroids contain this element. It would be easy to obtain sufficient material free from contamination if the external glandules were selected for investigation. On the other hand, the internal glandules would present great difficulties, and great care would have to be exercised in order to obtain parathyroid quite free from thyroid.<sup>2</sup>

<sup>1</sup> Small quantities of iodine are found in the thymus and the pituitary. Drechsel (121) found iodine in organic combination in the horny skeleton of *Gorgonia cavolinii*, and on decomposing obtained a crystalline amido-acid ("iodogorgonic acid"),  $C_4H_5NIO_2$ . The same observer also records the discovery of iodine in the hair of a patient who had been treated with iodide of potassium. He also confirmed the existence of Baumann's thyriodin and of Frankel's thyreo-antitoxin (168, 169), and added the discovery of another crystalline basic substance.

Wheeler and Mendel (635) recall the fact that Drechsel's iodogorgonic acid from Gorgonian corals was shown by Wheeler and Jamieson (634) to be 3 : 5 di-iodotyrosin. In sponges it is now shown that the iodine is present in the same form. The ease with which iodine enters into combination with the aromatic group is worth noting in regard to the function of iodine in protein combination in the thyroid.

<sup>2</sup> Other recent papers on the chemistry of the thyroid are: Nardelli (425), Claude et Blanchetière (87), Juschtschenko (293), Hunt and Seidell (274), Claude and Blanchetière (87) make the interesting observation that a thyroid may be rich in iodine and yet contain no colloid.



#### N. The Immuno-Chemistry of the Thyroid Apparatus.

Fassin (157), working with thyroidectomized dogs and rabbits, finds a marked diminution in the hæmolytic as well as the bacterial alexine.

Marbé (357) states that administration of thyroid substance by the mouth in the human subject and in animals raises the opsonic index. Injection of aqueous extracts also determine, after some hours, a very considerable opsonin increase. Thyroid feeding brings about also an increase of the phagocytic properties of the leucocytes in men and animals.

Extirpation of the thyroid brings about, as does myxœdema, a reduction in the phagocytic power of the leucocytes and in the opsonic index. This parallelism has induced the author to use the term "phagopsonic index."

The action of the thyroid on the phagopsonic index is only shown after a certain latent period. The action of the thyroid on the phagocytic properties of the leucocytes can be better demonstrated *in vitro* than *in vivo*. The reaction of the blood-serum in "hyperthyroid animals" is more strongly acid, in "athyroid" animals less strongly acid, than normal.

As pointed out by Fjelstad (160), these experiments of Marbé concern the normal opsonins and complements, not the opsonins and complement in active immunity. Fjelstad finds that removal of the thyroids from the rabbit does not—at least, during the first month—appreciably affect the formation of immune bodies (more specifically the agglutinins). It is therefore probable that any increased susceptibility to infection in such animals must be due to causes other than the depression of the immunity reactions.

Laser (323) records benefit in four women suffering from exophthalmic goitre after the use of Möbius's "anti-thyreoidin."

Edmunds (136) concludes that antithyroid preparations in equal doses with thyroid as tested upon animals produce no effect in preventing the ill-effects of thyroid excess, though he reports improvement in Graves's disease after use of the Möbius antithyroid serum, but especially after the administration of milk obtained from thyroidless goats (138 ; see also 137).

**O. The Influence of the Thyroid upon Metabolism.**

In the treatment of myxœdema and different forms of goitre, a rapid loss of weight is noted on feeding with thyroid-gland substance [Leichtenstern (328)]. This is partly due to loss of subcutaneous tissue, partly to loss of water. Thyroid preparations are used with good results to reduce obesity [Leichtenstern u. Wendelstadt (329), Davies (116)]. In order to explain these effects, several series of experiments have been performed, with the object of directly studying the influence of the administration of thyroid glands upon metabolism.

The experiments of Ord and White (438), Mendel (388), Napier (424), and Vermehren (605), pointed to a distinct increase of nitrogen in the urine, with a concomitant decrease in weight, pointing to increase of protein metabolism. But all these experiments were of short duration, and the total intake and the total output were not accurately determined.

Similar results were obtained by Dennig (118), Bleibtreu and Wendelstadt (49), Bürger (62), Roos (502), Zum Busch (64), Dinkler (119), and Georgiewsky (180). The duration of the experiments here were at most fourteen days.

Other workers have found little or no increase in nitrogen excretion—*e.g.*, Ewald (152) in a case of myxœdema. Scholz (536) and Richter (488) found a very small increase in the amount of nitrogen excreted. The nitrogen balance remained positive.

The discovery of iodine in the thyroid gland by Baumann (20), and the belief that thyroiodin was the "active principle," led observers to test the action of this last upon metabolism instead of the crude gland. Treupel (583), Grawitz (202), David (114), Dinkler (119), experimenting on the human subject, and Roos (500, 501), who used a small dog, came to the conclusion that thyroiodin influences metabolism in the same way as the thyroid-gland substance itself, in that the body weight diminishes and the nitrogen excretion increases.

Some experiments of short duration are recorded, with the object of estimating the oxygen taken in and the carbon

dioxide given out during thyroid administration. Magnus-Levy (354) found in a normal man during exhibition of thyroid glands a not very distinct increase of the oxygen intake and the carbonic-acid output. Later experiments by the same author (355) upon a myxœdematous patient gave, on the other hand, an increase of 80 per cent. in the oxygen intake under the influence of thyroid, and 43 per cent. under the influence of thyroiodin.

The experiments of Stüve (565) on a healthy man showed an increase of oxygen intake of 20 to 23 per cent., and a somewhat smaller increase of carbon-dioxide excretion. Thiele and Nehring (574) also found an increase of oxygen intake amounting to 20 per cent.; the carbon-dioxide output was smaller and irregular. These experiments were performed upon healthy men.

The distinct increase of oxidation processes shown in these experiments proves that the greater part of the loss of weight under the influence of thyroid administration is caused by loss of fat. The question as to whether the protein is also used up remains unanswered, for the experiments are of too short a duration to exclude the possibility of the increased nitrogenous excretion being due to an increased excretion of urea and other nitrogen-containing compounds already stored up in the organism.

Schöndorff (533) performed a series of very careful experiments of long duration upon dogs, and came to the conclusion that metabolic processes are distinctly increased by the administration of thyroid substance. There is at first no influence on protein metabolism, but an increase in nitrogenous excretion from increased elimination of nitrogen-holding extractives already present in the body. The body fat was first used up. After a certain period, however, the protein was also attacked. On stopping the thyroid administration, the metabolism returned to normal, while renewed administration led to no increased nitrogenous excretion.

As regards the relation between the iodine content of the thyroid and its effects upon metabolism, Roos (502) recorded the results of three experiments upon a dog. In the first experiment the administration of 5 grammes of dried children's thyroid containing 0.025 per cent. of iodine had scarcely any effect upon the nitrogenous excretion or

upon the body weight; later, the administration of 5 grammes of children's thyroid, containing 0.18 per cent. of iodine, caused an increase in the excretion of nitrogen of about 10 per cent. In the second experiment, also, a greater effect was produced by the administration of the thyroid containing the larger percentage of iodine. In the third experiment, in which the dried thyroids of dogs were administered, 5 grammes of a preparation containing no iodine had no effect, whereas 5 grammes of a preparation which contained 0.35 per cent. of iodine was followed by a distinct increase in the nitrogen excretion and a slight loss of weight.

. Oswald (440, 441) found that thyreoglobulin poor in iodine produced little or no effect upon metabolism, while thyreoglobulin rich in iodine produced a marked increase in the nitrogen excretion. Thyreoglobulin from hog thyroid containing 0.5 per cent. of iodine seemed more active than that of the human thyroid with 0.3 per cent. of iodine (441).

Marine and Williams (365) have recently reported two experiments on the effects of feeding dogs with dried sheep thyroid containing varying proportions of iodine. Of one preparation which contained 0.0292 per cent. of iodine, 11 grammes administered to a dog caused no loss of weight in eighteen days, and the fresh thyroid of the dog on analysis yielded but 0.173 milligramme of iodine per gramme. The second preparation contained 0.1092 per cent. of iodine. The dog, which received 11 grammes of this, lost 454 grammes weight in eighteen days, and its fresh thyroid contained per gramme 0.439 milligramme of iodine.

These experiments with substances extracted from thyroid glands are not very convincing, but in a general way they point to the conclusion that preparations of thyroid, as well as thyroid itself, produce an effect on metabolism which bears some relation to the iodine content.<sup>1</sup>

The effects of thyroid and parathyroid administration

<sup>1</sup> Breisacher (58) states that all dogs from which the thyroid has been removed die when fed upon meat or meat broth, while 30 per cent. of the animals fed upon milk and eggs remain normal. This has led physicians to treat various diseases of the thyroid, such as myxœdema and Basedow's disease, by prescribing a diet consisting chiefly or entirely of milk, eggs, and vegetables. This beneficial result of a milk diet, however, was not obtained by Ughetti (586). According to Lanz (323), the subcutaneous injection of thyroid juice in normal animals brings about atrophy of the gland.

upon metabolism has been studied by Easterbrook (123, 124, 125) in patients suffering from mental diseases. This observer has found that there is considerable loss of weight, some pyrexia, and increased perspiration. The blood showed diminution in the hæmoglobin, and to a greater extent in the red cells, and slight leucocytosis. There were headaches, pains, tinglings, and prickings, as well as tremors of face, fingers, and limbs. There was also weakness and a feeling of exhaustion. The urinary nitrogen was much increased. The thyroid acted, in fact, as a profound katabolic stimulant. The parathyroids produced no effects.

Bircher (47) has published the result of a series of experiments, which show that the administration of thyroid substance promotes the growth of bone in the normal animal. He concludes, therefore, that the favourable influence of thyroid preparations upon bone growth in cretinism is not of a specific nature.

According to the majority of authors, the calcium content of the urine is raised after parathyroidectomy, while that of the brain and the blood is lowered. Cooke (90) cannot confirm this; on the other hand, he found an increase of Ng in the urine. The total N and  $\text{NH}_2$  coefficient is raised. In intermediate metabolism the organism probably gives rise to substances of an acid nature, which are rendered harmless by the secretion of the parathyroids. If the secretion be absent, then Ca or Mg are employed for a similar purpose. Tetany even may be regarded as due to deficiency in these elements [*cf.* Morel (406), p. 307].<sup>1</sup>

It is alleged that parathyroidectomy hinders the healing after fracture of bone in young animals [Morel (405), Canal (66); see, however, Jovane and Vaglio (292)].

## P. The Physiological Effects of Extracts of Thyroid and Parathyroid.

### 1. *Immediate Results.*

The extraordinary physiological effects produced by the intravenous injection of extracts of the medulla of the adrenal [Oliver and Schäfer (436)] and of the nervous por-

<sup>1</sup> See also a further paper by Cooke (91).

tion of the pituitary [Howell (266), Oliver and Schäfer (435)], have led to numerous experiments with extracts of very many organs and tissues. Some account of these investigations has already been given (p. 24 *et seq.*).

Extracts of thyroid gland, in common with those of the great majority of tissues and organs, produce, when injected intravenously, a lowering of the blood-pressure. This effect was first observed by Oliver and Schäfer (435), and was confirmed by Haškovec (231), Georgiewsky (181), Guinard and Martin (208), Fenyvessy (158), Ocaña (433), Svehla (570), and Patta (451), as well as by numerous other observers. The interest in the observation began to diminish as it became known that this depressor effect is common to extracts of all tissues and organs in the body [Osborne and Vincent (439), Vincent and Sheen (617), etc.].

Recently v. Fürth and Schwarz (172), Lohmann (239), and Gautrelet (179), have suggested that the depressor substance in thyroid extracts is choline. Now, the present writer has not investigated this matter in relation to the thyroid, but, as will be seen on reference to p. 26, it has been abundantly proved that in nervous-tissue extracts, although choline is present, the depressor effect must be due to other substances. It seems probable that the same will be found to apply to the thyroid extracts.

Some observers, however, record a pressor effect of thyroid extracts [Heinatz (234) and Livon (337)]. It is probable that not much importance is to be attached to these observations. The matter has been fully discussed in regard to tissue extracts generally (see p. 33).

As regards the effect of thyroid extracts upon the heart, Oliver and Schäfer (435) could observe no change in the volume and frequency of the pulse. Heinatz (234) noted a considerable increase in rapidity of the heart's action. Haškovec (231) attributes this to a stimulation of the accelerator nerves. Similar effects were observed by Guinard and Martin (208), and Svehla (570), while Livon (337) and Fenyvessy (158) obtained a retardation of the pulse. Ocaña (433) noted after injection of thyroid extracts an increase of the irritability of the inhibitory nerves.

But it is exceedingly probable that these effects upon the heart and bloodvessels are in no way specific, and bear no

relation to an internal secretion on the part of the thyroid gland.

Thyroidin, according to Cyon and Oswald (112), stimulates the intracardiac inhibitory centres in dogs and rabbits, although several other observers, including v. Fürth and Schwarz (172), can obtain no such result. In these animals, also, Cyon and Oswald are of opinion that thyroidin acts as an antagonist to atropin. This view was supported by Boruttau (56), Ocaña (433), Besmertny (36), and Coronedi (94). Harnack, however (229), pointed out that, even after large doses of atropin in the rabbit, the paralytic effect on the vagus is very transitory, so that, on injecting thyroidin, it is easy to suppose that this substance has acted as an antagonist. This explanation of the phenomenon is adopted by Fenyvessy (158), Isaac and R. v. d. Velden (278), and v. Fürth and Schwarz (172).

On the cat thyroidin produces very marked effects. After injection of 0.2 to 0.3 milligramme there is a rapid fall of blood-pressure and a large, slow pulse, lasting for a minute. This is due to stimulation of the vagus centre in the medulla, and disappears on section of the vagi, or after the administration of atropin. The fall of blood-pressure is due to a direct action on the heart [v. Fürth and Schwarz (172), v. Fürth (171)]. These effects have, in all probability, no relation to any specific function on the part of the thyroidin.

Mathes (369) states that thyroid-juice hastens coagulation of the blood *in vitro*; but it shares this property with many organs in the body.

## 2. Chronic Results.

Long-continued artificial inundation of the organism with thyroid ("hyperthyreoidization") gives rise to a train of symptoms which has been supposed to shed some light on the pathology of exophthalmic goitre (Graves's disease, Basedow's disease).

The most striking and the most constant of the symptoms produced is acceleration of the pulse. This is recorded by Ballet and Enriquez (15, 16), Canter (69), Lanz (320), Georgiewsky (181), Hellin (236), v. Fürth and Schwarz (172), and others, upon dogs and rabbits; by Angiolella (8) and Lüdke (342) upon guinea-pigs; by Lépine (333) upon a

goat ; by Peiser (453) upon rats ; by Edmunds (133) upon monkeys ; and by v. Fürth and Schwarz upon cats.

Among other symptoms which have been noted are flushing, tremors, sensation of heat, perspiration [Johnston (287)], exophthalmos [Gagnevin (176), Ballet and Enriquez (15), Cunningham (106)].

In monkeys, Edmunds (133) found that the administration of large doses of thyroid extract produces marked results—viz., proptosis, dilatation of pupils, widening of palpebral fissures, erection of hairs on the head, the hair falling out in patches, paralysis of one or more limbs, emaciation and muscular weakness, and, finally, death from asthenia. The average life of the monkeys after the commencement of this treatment was seventy-six days. Of the above effects, those produced on the eyes are, according to Edmunds, caused mainly by action through the cervical sympathetic.

Thyroidin produces similar effects upon the circulation, but the general result is not so suggestive of exophthalmic goitre as is that obtained by thyroid treatment. The general conclusion seems to be warranted that, in all probability, morbus Basedowii is due to hyperthyroidization, and that thyroidin does not represent the active principle, or all the active principles, of the thyroid gland.

### 3. *General Medical Employment of Thyroid Extract.*

In addition to its use in myxœdema, cretinism, and other cases where there is presumably a certain amount of thyroid insufficiency, thyroid extract has also been employed in many other affections. Its employment in obesity has already been referred to. It has also been used with some success in rheumatoid arthritis [Wilson (642), Middleton (395)],<sup>1</sup> in infantile wasting [Simpson (553)], and in goitre.

Thyroid medication has also been used in cases of delayed union of fractured bones [Gauthier (178), Bayon (29)], in osteomalacia, and in rickets. It has been recommended in infantilism, in acromegaly and gigantism, in chorea [Roden (495)]<sup>2</sup>, in serum rash and serum sickness, in diphtheria [Hodgson (249)], and in carcinoma [Jones (289)].

<sup>1</sup> See also Steele-Perkins (561).

<sup>2</sup> See also Giambi (183), and Vidoni (809), who used "Parathyroidin Vassale."



### Q. Artificial Renewal of Thyroid and Parathyroid Secretion.

#### 1. *By Grafting.*

There can be little doubt that the leaving behind of a thyroid lobe, or even, according to the majority of authors, a very small shred of thyroid tissue, will suffice to keep an animal in good health. This naturally led to experiments in the direction of grafting. Schiff (391), who was the first to perform in a systematic manner extirpation of the thyroid, was also the first to attempt grafting. But his grafts *qua* grafts were not successful [Cristiani (100)]. He, however, states that he succeeded in prolonging the life of his dogs after thyroidectomy; but this success may have been due to the temporary supply of thyroid secretion furnished by the gland substance, and analogous to a subcutaneous or intravenous injection of thyroid extract, or to a process of feeding with thyroid substance. Schiff operated upon dogs with the thyroids of other dogs two to five weeks before performing thyroidectomy. The grafts did not "take," and were gradually absorbed. Since the time of Schiff very numerous grafting experiments have been performed. Kocher (301) relates that he had, in 1883, attempted grafting in the human subject after ablation, and with some temporary benefit. The grafting experiments in the hands of numerous observers were for a long time unsuccessful [Carle (74), Drobnick (122), Zuccaro (652, 653), Eiselsberg (139), Ferretti (159), Sgobbo and Samari (544), Canizzaro (68), Ughetti (585), Montandon (404), Bouchard (57)].

It was not until the date of Eiselsberg's second publication (140) that any really satisfactory grafting experiments were recorded. This author found that in four cats the operation was completely successful, both from an anatomical and a physiological standpoint. A little later appeared a series of papers by Cristiani (97, 98, 99, 100), who was equally successful in sixteen out of nineteen rats in his earlier series of experiments, and who afterwards performed a very large number upon many different species of animals. Pantaleone (448, 449) was not so successful,

while Munk (418) was only partially so. Enderlen (146) and Sultan (568) obtained fairly good positive results. Cristiani (100), by taking special precautions, succeeded in thyroid grafting in all species of animals in which he tried it. In order that the graft should be successful, it is necessary that the organ transplanted should not be too voluminous. For small animals (rats, young weasels, etc.) one can graft entire lobes of the gland; but for larger animals it is necessary to divide the organ into flat or elongated slices. The thyroid graft carried out under these conditions and with the surgical precautions detailed by Cristiani not only does not become absorbed, but actually increases according to the needs of the organism into which it has been grafted. Grafting may succeed not only when performed into a different part of the body of the same animal, but also between different individuals of the same species, and sometimes also between different species, and even families [Cristiani (101)].

Horsley (264) suggested that grafting should be tried in man to arrest the progress of myxœdema. This was carried out with partial success by Bircher (41, 42, 43), and by Bettencourt and Serrano (37). But, as in the case of Schiff's grafting experiments, the grafted gland was in most cases absorbed, and the beneficial effects were not permanent. Only in one case has the improvement lasted for more than a few months. This was in a case of myxœdema recorded by MacPherson (353), in which all the symptoms disappeared after the operation, and had not returned three years later.

In the experiments referred to above, the graft was probably in most cases a "thyro-parathyroid" graft. A considerable amount of work has now been carried out in the direction of pure parathyroid grafts. V. Eiselsberg, in the experiments above referred to, grafted (140) parathyroids along with thyroid, and found that after extirpation of the grafted gland tetany supervened. This is explained, according to the view held by many modern writers, by removal of the parathyroids. This is, for example, expressly stated by Halsted (222). But if, as urged previously, merely the slight damage done to the thyroid by handling will cause fatal tetany, then surely

this result would not be unexpected when the thyroid is totally removed. To assume that death in this case was due to removal of parathyroids is simply begging the question.

Enderlen (146) in 1898, and Payr (452) in 1906, transplanted, with morphological success, the parathyroids, as they happened to be included in the thyroid grafts. Transplantation of the isolated parathyroid glands was performed by Camus in 1904. Parathyroid grafts have also been successfully carried out by Cristiani (99, 102, 345), Cristiani and Ferrari (103), and Lusena (344).

Leischner (330) reports successful transplantation of the parathyroids in rats.

Halsted's experiments were commenced in 1906, and various kinds of successful grafts of the glandules have been carried out.

Pfeiffer, Hermann and Mayer (461) have made two successful autotransplantations in puppies. Biedl (38) reports two successful cases in which "foreign" parathyroids were grafted into the spleens of dogs. Halsted (122) "cannot quite credit" these observations for several reasons, which he states. Among these reasons one is that Professor Biedl did not create parathyroid deficiency either prior to or at the time of the transplantations.

Halsted believes that, in order that autotransplantation may succeed, it is necessary to create a parathyroid deficiency. Isotransplantation was always successful. Parathyroid tissue transplanted in excess of what is urgently required did not live.

Cimorini (84), working with large dogs, has grafted all four parathyroids into the peritoneal cavity of the same animal from which they were extirpated. This graft, as a rule, hindered the acute symptoms of parathyroidectomy. The peripheral zone of the grafts functioned for a limited time and then died. The interesting feature of these experiments lies in the fact that, when the grafts had been completely absorbed, the animal showed, *not* tetany (supposed to be due to parathyroid insufficiency), but *chronic symptoms* of cachexia (ordinarily supposed to be due to thyroid insufficiency).

Successful transplantation of parathyroids in the human

subject in cases of "tetania parathyreopriva" have recently been reported [Danielsen (113), Krabbel (312)]. (See p. 345.)

As a result of a renewed investigation upon rats, Leischner and Köhler (331) have come to the conclusion that the beneficial results obtained clinically may be explained on the hypothesis that parathyroid shreds left behind, although damaged, gradually resumed their function, while in the meantime the transplanted parathyroids (which finally became absorbed) hindered the occurrence of tetany.

### 2. *By Injection of Juice or Extracts of the Glands.*

Pisenti and Viola (466) appear to have been the first to employ experimental opotherapy with the thyroid glands. Vassale (591, 592) and Gley (187) found only a temporary benefit to accrue after thyroidectomy if the animal were subjected to an intraperitoneal injection of thyro-parathyroid juice. Gley believed that his unsatisfactory results were due to the fact that treatment was not continued for a sufficiently long period. But good results have not been obtained by all observers [Schwarz (541)], and, according to some writers, the extract, to be of any service, must contain *parathyroid* juice. It is, indeed, stated that pure thyroid extract is actually harmful after cases of extirpation of both organs [Pugliese (473)]. This observation may be compared with the statement of Lusena (345) and of Vassale and Generali (599), that the ill-effects of parathyroidectomy are relieved by thyroidectomy.

It has, further, been held that injection of parathyroid extract is of great benefit in preventing or postponing the symptoms due to absence of parathyroids [Moussu (414), Lusena (345)]. On the other hand, Pineles (463) reports that neither stomachic nor subcutaneous and intraperitoneal administration of parathyroids produces any beneficial effects after parathyroidectomy in cats.

Murray (421) successfully employed a glycerine extract of sheep's thyroid (now the liquor thyroidei of the British Pharmacopœia) in the treatment of monkeys after thyroidectomy. This author found that in some cases the symptoms disappeared, but in others there was only an improvement, and death afterwards ensued, with acute nervous symptoms. It is worth while noting in this relation that,

in the experience of the present writer, death from nervous symptoms has only occurred once out of thirteen monkeys, and in this case there is reason to believe that this had nothing to do with extirpation of the glands. Had these animals been treated with thyroid substance at this time, we might have supposed that their complete recovery and continued health were due to the treatment.<sup>1</sup>

Murray suggests that when death ensued with nervous symptoms during treatment, the parathyroids were extirpated along with the thyroid, while in the former they were left behind. But in most common species of monkeys, at any rate, the parathyroids are so placed as to be practically certain to be removed along with the thyroids. He further says that it is not surprising that the parathyroid symptoms are not relieved by thyroid treatment. But it must be borne in mind that the thyroid extract would contain also parathyroid substance. Murray does not state, at any rate, that the parathyroids were cut away before the extract was made. The supporters of the view that the parathyroids possess a separate functional importance would urge that more parathyroid material is required when administered in this manner than would be naturally included in the extracts.

### *3. By Administration of Thyroid and Parathyroid Substance by the Mouth.*

Although, as will be gathered from the foregoing account, the present writer has not been able to confirm the statement of Horsley and his successors in this line of work, Murray and Edmunds, that removal of the thyroids from monkeys induces myxœdema, yet there can, of course, be no doubt that the animals are considerably affected by the operation. There seems no doubt, further, that they were improved in condition by thyroid treatment to such an extent as to encourage further inquiry, both experimental and clinical. These inquiries led to the employment of thyroid given by the mouth in the treatment of myxœdema. Simple feeding with the actual glands was advocated by Howitz (267), MacKenzie (352), and Fox (167).

<sup>1</sup> Halpenny and Gunn (219) obtained rather different results. See, however, on the subject of periodicity of symptoms, a discussion on p. 308.

But the method of giving the simple fresh gland had many disadvantages. Many patients found it hard to accept either the raw or the cooked glands. Then, too, it was often difficult to be sure that the patient was really receiving the thyroid gland. Thymus, submaxillary, etc., must often have been given instead of thyroid. Again, it was felt necessary to be able to standardize the drug, so that a definite dose could be given, and the variability of effect of different thyroid glands might be overcome. It is, however, probable that the most active thyroid preparation is the fresh gland.

The dried substance, pills, and tabloids have all been employed. The question as to thyroïodin and the active principle has already been discussed (p. 327).

Although the condition of animals deprived of their thyroid cannot be correctly described as myxœdema, yet this may be notably improved by the administration of thyroid substance. Vincent and Jolly (616) report that the nasal catarrh, conjunctivitis, and loss of weight of cats were all considerably relieved by giving thyroid substance.

Further accounts of thyroid therapy will be found in the works of Shaw (545) and Waller (623).

#### R. Functional Changes in the Thyroid.

In a dog which had been subjected to a few days' inanition, the thyroid (hardened in Fleming's fluid) appeared very different from the normal. The cells appeared swollen rather than proliferated, and in some cases the vesicles were filled with cells instead of colloid. The vesicles were shrunken into various shapes, and there was a large amount of intervesicular tissue. The general appearance of the section was as if the gland had been roughly squeezed, so that the vesicles were any shape other than spherical. The change wrought by inanition seems to make the structure of the gland tend towards that of parathyroid [F. D. Thompson (576)].

Missiroli (398), who worked with rabbits, seems to have obtained quite different results. According to this writer, if one ceases to administer food, the colloid material becomes stored in the vesicles, and distends them. On return to a normal régime, the follicles once more empty themselves.

The same author also reports (398) that, after section of the cervical sympathetic in rabbits, there is a marked production of granules in the thyroid cells and an accumulation of colloid in the vesicles.

The whole subject of physiological changes in the thyroid under varying conditions is urgently in need of systematic investigation.

The thyroid of a meat-fed dog differs in no way from the



FIG. 75.—Thyroid of dog, killed after a few days' inanition. Cf. with Fig. 77, taken from a normal dog. In the inanition thyroid there is a marked increase of intervesicular tissue, and a distortion, shrinkage, and occlusion of many of the colloid vesicles.

*e. interves.*, intervesicular epithelial tissue; *c. ves.*, colloid vesicle.

normal, while that of a dog fed on cereals tends to some extent towards the condition found in inanition.

Chalmers Watson (624, 625) describes a very marked hypertrophy of thyroid and parathyroids in the fowl after treatment with an exclusive meat diet. He further reports, in the second generation of meat-fed rats, entire absence of colloid, and little or no attempt at vesicle formation. He admits that the results obtained were very variable, but he considers that they show that an excessive meat diet induces structural changes in the thyroid gland. It is not unreasonable, perhaps, to suppose that such might be the case,

but Watson's observations by no means prove it, for it has been pointed out by Forsyth (165) that there is great variation in the appearances of thyroids of the same species of birds. Mrs. Thompson (576) further suggests that many of the changes described by Watson as due to the excessive protein diet are in reality due to inanition, the structural effects of which are described above.<sup>1</sup>

**S. Changes in the Thyroid after Parathyroidectomy.**

Edmunds (134) describes certain changes in the thyroid after parathyroidectomy. The histological changes, he says, are identical with those described as "compensatory

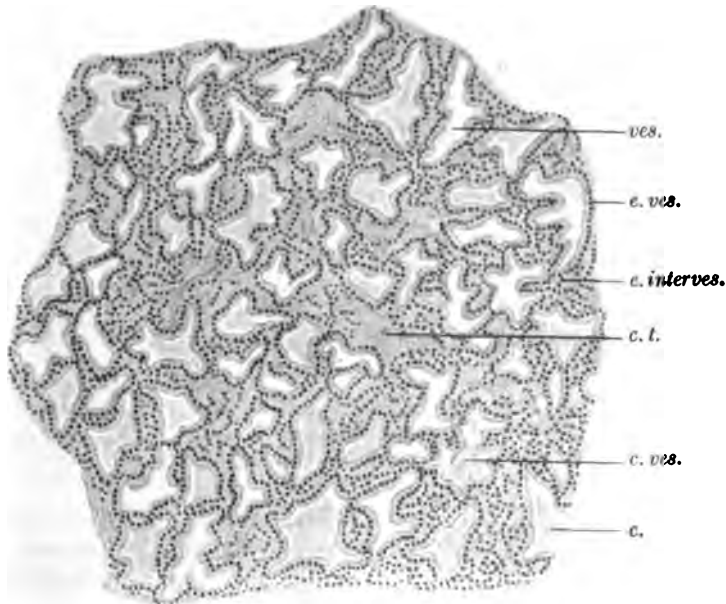


FIG. 76.—Thyroid of dog, thirty-two days after removal of all four parathyroids. The vesicles have become very irregular in shape, and there seems to be an increase in the interveticular epithelial tissue. Cf. with Figs. 68, 69, and 71.

*ves.*, vesicle; *e. ves.*, epithelium lining vesicles; *e. interves.*, interveticular epithelial tissue; *c. t.*, connective tissue; *c. ves.*, colloid vesicle; *c.*, colloid.

hypertrophy," but the thyroid, as a whole, does not enlarge, but, on the contrary, sometimes becomes smaller.

A cat from which the thyroid lobe (including its para-

<sup>1</sup> See also Tanberg (573).



thyroids) on one side and three parathyroids only on the other side had been removed, was allowed to live nearly a month. At the end of this period it was sacrificed, and the remaining thyroid lobe examined. The thyroid had atrophied, and on histological examination very little true thyroid structure was found to have persisted. There were vesicles in some parts of the tissue, but these were few and far between. There was a large amount of tissue indistinguishable from normal parathyroid, and a still larger

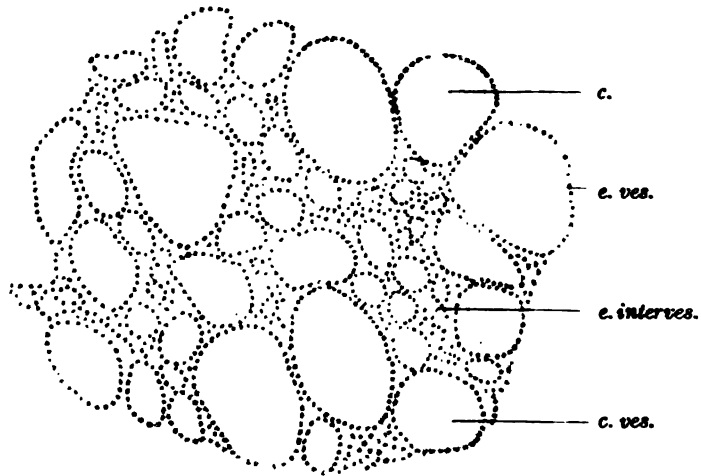


FIG. 77.—Thyroid of normal dog. ( $\times 120$ .) Cf. with Figs. 68, 69, and 70.  
*c.*, colloid; *e. ves.*, epithelium lining vesicles; *e. interves.*, epithelial intervesicular tissue; *c. ves.*, colloid vesicle.

amount of which it would be impossible to say to which category it belonged. This cat showed no symptoms. In another cat, in which an analogous operation had been performed, but which died with typical symptoms within five days, still more extensive structural changes were found in the thyroid.

Similar changes were observed in the thyroid of the dog after extirpation of all four parathyroids (Fig. 68).

Changes in the parathyroid after removal of the thyroid will be described in the following section.

### T. The Relationship between Thyroid and Parathyroids.

This has been a much-discussed and much-disputed question from the time when the parathyroids were first discovered, and the matter cannot yet be considered as settled.

It will be fitting to introduce the discussion of this part of our subject by giving a brief history of the discovery of the parathyroids.

Remak (483) discovered in kittens near the upper end of the thymus small bodies which he called "Wimperblasen der Thymus." This appears to have been a parathyroid. At any rate, this is the opinion of Kohn (308, 309) and other writers. In 1864 Virchow (620) described small bodies near the thyroid which he considered as "accessory thyroids," or lymph glands. Some of these bodies may, of course, have been true accessory thyroids, but from the marked constancy of their occurrence it is exceedingly probable that they were parathyroids.

In 1880 Sandström (514) described "a new gland in man and various mammals." This was apparently the external parathyroid in dogs, cats, etc., and the posterior inferior body in the human subject.<sup>1</sup>

It is to Sandström that we owe the term "glandulæ parathyroides." He found the glandules constantly present in fifty human subjects examined by him. In situation, size, form, and colour they exhibited great variety. The two glands were always found in the immediate neighbourhood of the thyroid on each side, on the posterior surface of the lateral lobe, or close to its inferior border. Often both were found in close proximity to the inferior thyroid artery, from which they received their blood-supply.

The gland was made up of solid masses of cells, divided into lobules by connective tissue. The cells contained fat particles, and probably, also, colloid. There were many variations in the arrangements of the gland substance [A. Kohn (308, 309)]. Among lower animals, the dog, cat,

<sup>1</sup> This is the conclusion I have reached from a perusal of an abstract by Retzius in Hofmann-Schwalbe's "Jahresb." (514), and by Berger in Schmidt's "Jahrb." (514). The original is in the Swedish language. It is difficult to understand why Sandström should have only seen two parathyroids in the human subject, as all four are "external" (see p. 249).

horse, ox, and rabbit were investigated, and in all these species the gland was constantly found. The glands belonged to the same group of organs as the thyroid. All the variations in their structure corresponded to different stages of thyroid development; they were, indeed, embryonic material destined to form thyroid tissue.

In the same year Baber (14), unaware of Sandström's work, described and laid much stress upon "undeveloped portions" of the thyroid gland. These he found in the dog, kitten, sheep, seal, and in the rook and the pigeon. They were "distinct bodies, not continuous with the normal gland tissue, but separated from it by layers of connective tissue, and frequently lying in depressions on the surface of the gland." He gives a very good low-power microscopic drawing of a parathyroid.

Horsley (261), unacquainted with Sandström's discovery, reinvestigated the "embryonic tissue" of Baber. He described it as composed of columns of cells, round which blood capillaries course. The tissue has a mesh-like aspect. In some animals a large quantity of this tissue could be found in a single lump beneath the capsule, separately encapsuled. Horsley was not inclined to the view that this tissue ever developed into proper thyroid tissue.

Wölfler (645) and Rogowitch (498) described embryonic cell masses in the thyroid, for the work of Sandström, Baber, and Horsley fell into almost complete oblivion. The only other references to the parathyroids at this period are by Krause (314, 315) in his textbooks.

In 1891 Gley (185D) rediscovered the parathyroids. In his preliminary note on the effects of extirpation of the thyroid in the rabbit, this author describes the parathyroids under the name "glandules thyroïdiennes." The observations were confirmed and extended by Cristiani (95, 96) and Nicolas (428, 429, 430). This last author found in *Vesperugo pipistrellus* that there are always two parathyroids on each side.

All observers up to this time had considered the parathyroids to be embryonic stages of thyroid tissue. Kohn (308, 309) was one of the first to oppose this view, and his attitude was supported by the experimental results of Vassale and Generali (597, 598, 599), who urged the view

of the separate and supreme functional importance of the parathyroids.

Gley, who was originally the chief supporter of the view that the parathyroids develop into thyroid, subsequently abandoned this position, and substituted a theory of a functional relationship between the two kinds of tissue [Gley (196)]. This theory is based upon three kinds of proof: (1) *Chemical*: Gley found in the parathyroids of the rabbit about twenty-five times more iodine than in the thyroid, in the dog six times more, and suggested that the parathyroids prepare the secretion which is then stored in the thyroids, and utilized according to the needs of the economy. If the iodine be not rendered harmless by elaboration in the parathyroid (as when these are extirpated), we get acute symptoms. If the iodine be subjected to preparation in the parathyroid, but is not distributed to the body by way of the thyroid (as when this is extirpated), we get nutritive troubles from the absence of assimilable iodine in the body. (2) *Physiological*: Occasionally complete parathyroidectomy, leaving the thyroid *in situ*, gives rise, not to acute symptoms, but to slowly progressive changes in the bodily nutrition. Thus, we get symptoms commonly associated with thyroid insufficiency induced by absence of parathyroids. It is alleged by Lusena (345), and also by Vassale and Generali (597, 598, 599), that parathyroidectomy kills more rapidly than thyro-parathyroidectomy. This is explained by Vassale and Generali by supposing that, when the parathyroids are removed, the animal is in a toxic condition, which is the more marked when the nutritive changes of the body generally are more pronounced. The tetany then will be more or less serious, according as the thyroid is more or less active, and therefore, logically, will be much less marked after ablation of the thyroid. (3) *Histological*: According to Edmunds (133, 134), and Vassale and Generali (597, 598, 599), there is a disappearance of the colloid substance in the thyroid after removal of the parathyroids.

The theory of a functional relationship between thyroid and parathyroid is also held by Jeandelize (284). The majority of writers, however, appear to prefer to consider the two bodies as quite distinct, both morphologically and physiologically.

The present writer, in conjunction with Professor W. A. Jolly (615), found that, on microscopic examination of parathyroids left *in situ* after removal of the thyroid, a conspicuous alteration in structure occurs. This presented itself at first as a difficulty in recognizing whether small structures which had been left behind were thyroid or parathyroid. Later, we became convinced that these were intermediate in character between the two. Now we are compelled to adopt the view that parathyroid tissue,

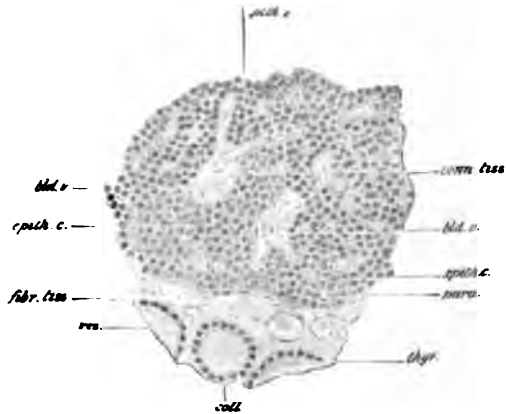


FIG. 78 shows a small portion of parathyroid of a cat embedded in thyroid tissue. It is seen to consist for the most part of solid columns of epithelial cells with strands of vascular connective tissue. A thyroid vesicle and portions of two others are shown in the lower part of the figure, separated from the parathyroid by a fibrous-tissue capsule. (Drawn by Dr. Thomas Lewis.)

Lettering common to Figs. 78, 79, 80, 81. *bl. v.*, bloodvessels; *coll.*, colloid; *col. epith. c.*, columnar epithelial cells; *conn. tiss.*, richly vascular interstitial tissue; *d.*, debris of cells; *epith. c.*, solid columns of epithelial cells; *fibr. tiss.*, fibrous boundary between thyroid and parathyroid; *para.*, parathyroid; *prim. ves.*, irregular or cleft-like openings, being the first stage in the development of thyroid vesicles; *thyr.*, thyroid; *ves.*, vesicles.

when left behind, approximates in appearance to ordinary thyroid tissue, so that the final product in some cases cannot be distinguished from the latter (see Figs. 78, 79, 80, 81).

Viguiet (610B) has recently reported that in a lizard (*Uromastix acanthinurus*, Bell) there are changes in the parathyroids after thyroidectomy. These changes indicate hyperfunction, but there is no formation of colloid.

As has been stated above, Vincent and Jolly regard thyroid and parathyroids as a single physiological apparatus,

the two kinds of tissue being intimately associated embryologically, and working together physiologically. In later papers (612, 613) the present writer has laid stress upon the fact that the two structures are derived from very similar

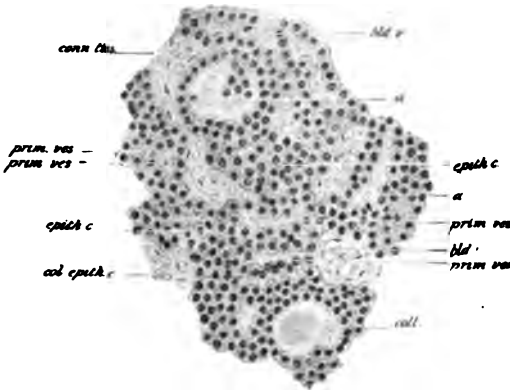


FIG. 79 represents a section of a portion of parathyroid of a cat which had been left behind after removal of both thyroid lobes, examined several weeks later. There are to be seen in various parts of the section numerous irregular or cleft-like spaces with regular boundaries of epithelial cells, which are sometimes of a columnar form. These spaces may either be empty or may contain cellular debris or colloid material. This, in fact, represents the first stage of transition from parathyroid to thyroid.

Lettering same as for Fig. 78.



FIG. 80 represents a further stage in the development of parathyroid into thyroid. The vesicles are tending to become fully formed, but a large part of the section is still occupied by solid columns of cells. The vesicles are for the most part small, and some are still irregular in shape.

Lettering same as for Fig. 78.

sources, and even in the fully developed state there is no fundamental difference between the constituent cells.

These views have received strong support from the side of comparative anatomy and histology by Forsyth (164, 165).

This writer looks upon the parathyroids as essentially thyroïdal in nature, possessing no peculiar function, but engaged in the active secretion of the same substance as the thyroid gland. He describes transitional and intermediate types of gland.

Forsyth's views largely agree with those of Mrs. Thompson (576), who has investigated the subject from a widely comparative standpoint. She is not prepared, however, to admit that parathyroids "are part of the main thyroid gland." To admit this conclusion would be to disregard the patient and brilliant work of Verdun, Maurer, and other embryologists. The parenchyma of the thyroid is by no means entirely made up of colloid vesicles. There is

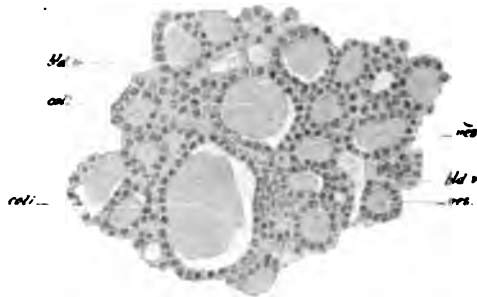


FIG. 81 represents a section of the normal thyroid of a cat. The vesicles are larger, and the intervesicular tissue less in amount than in the preceding figure.

Lettering same as for Fig. 78.

a large though variable amount of intervesicular cellular material, whose constituent cells do not differ in any important respects from those lining the colloid vesicles. This tissue is to all intents and purposes identical with that of the parathyroids, and instances of tissue continuity and gradual transitions and intermediate types from thyroid to parathyroid are described. In perhaps the majority of cases the transition forms are best seen between thyroid and internal parathyroid, though in the ox and the human subject such transitions are shown to exist between thyroid and external parathyroid (see Figs. 69, 72, and 73). Further, it was the external glandules in the experiments of Vincent and Jolly which, after removal of the thyroid, became converted into a tissue resembling the latter (see Figs. 78 to 81).

So that, although some authors have been inclined to look upon external and internal parathyroids as separate and distinct organs, the observations of F. D. Thompson do not lend any support to the view that either one is less intimately connected with the thyroid than the other [F. D. Thompson (576)].

The same author, however, points out that the nature of this relationship is by no means clear. It seems to be well established that the parathyroid glands are developed from the epithelium of the third and fourth gill-clefts, while the thyroid is derived from a median rudiment from the ventral wall of the embryonic pharynx. Moreover, the two structures do not arise at the same time, and embryologists are usually content to state that parathyroids only enter secondarily into relation with the thyroid. The primitive epithelial outgrowths constituting the buds of the thyroid and parathyroid, thymus, and other branchial cleft organs, cannot be very different from each other. Thus, the material of the thymus when first laid down is indistinguishable from that of parathyroid, and if for any reason in any particular species the usual lymphatic metamorphosis did not occur, the tissue would probably be looked upon as parathyroid, if its point of origin were not definitely known. However this may be, there seems no escape from the conclusion that in mammals the thyroid and parathyroid tissues are related to each other, and that the connections are not only physiological, but also anatomical.

Kishi (298) alone among recent writers sustains the embryonic theory in Sandström's original sense.

In the lower vertebrates thyroids and parathyroids appear to be separate and distinct, developed separately and at different times, and never coming into intimate relation with each other either anatomically or (so far as our present knowledge goes) physiologically. But in birds and mammals the parathyroid glandules enter into a peculiar relationship with the thyroid. They lie in close contact with it—on, or, indeed, actually within, its substance—and their solid epithelial columns tend (especially in the case of the internal body) to merge gradually into the (thyroid) tissue immediately surrounding it with its colloid vesicles. Moreover, when the thyroid is removed, the remaining parathyroids



may take on its function and change their structure accordingly [F. D. Thompson (576), Vincent and Jolly (615)]. Halpenny and Thompson (218) have recently obtained in the dog results fully confirming those recorded by Vincent and Jolly in the case of the cat (see Figs. 70, 71, 72, 73). From a dog both thyroid lobes and the two internal parathyroids were removed, leaving behind the external parathyroids on both sides. The animal lived without any untoward symptoms for eighty-three days, when a second operation was performed. The two parathyroids which had been left behind were found to have hypertrophied,

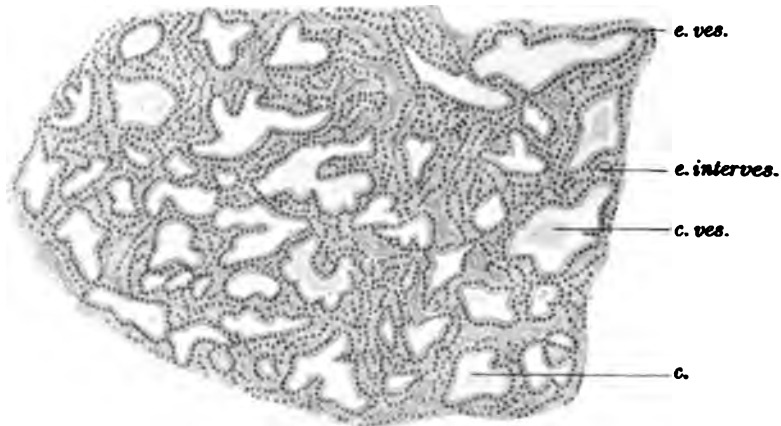


FIG. 82.—Parathyroid of a dog, eighty-three days after thyroidectomy, showing vesicles, some of which contain colloid.

*c. ves.*, colloid vesicle; *e. ves.*, epithelium of colloid vesicles; *e. interves.*, inter-vesicular epithelial cells.

and each of them showed on microscopic examination a number of irregular vesicles, surrounded by a layer of epithelial cells. Colloid was present in some of the vesicles. The appearance of the tissue is strikingly similar to that of the thyroid gland after parathyroidectomy (see Figs. 82 and 83, and compare with Figs. 76 and 77).

Edmunds (137) has recently performed a fresh series of experiments upon this subject. He has been unable to confirm the statements of the present writer and Professor Jolly and of Dr. Halpenny and Mrs. Thompson. But in his experiments he does not appear in any instance to have removed all the thyroid, and left the animal with only

one or more parathyroids remaining behind. Moreover, he admits that in one instance the parathyroid "may have been increased in size by two or three diameters, and may have undergone slight structural changes," though he says "it had certainly not become converted into thyroid tissue proper." Now, an increase of size of two or three diameters represents a very considerable hypertrophy. He does not state what the slight structural changes were, but his reference to "lymph spaces surrounded by secreting cells" is very significant.

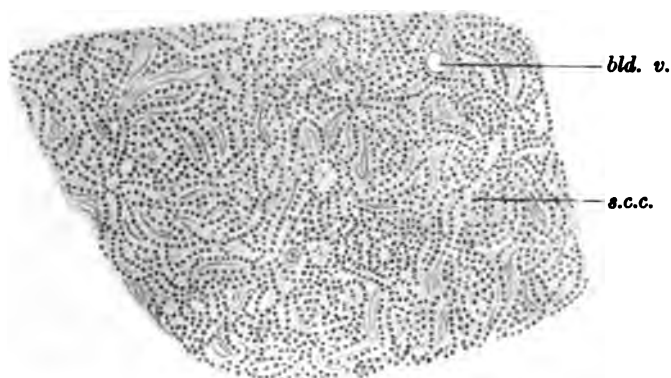


FIG. 83.—Normal parathyroid of dog. ( $\times 120$ )

s.c.c., solid columns of cells; *bld. v.*, bloodvessel. To be compared with Fig. 82.

Carlson and Woelfel (77) agree with the present writer and his fellow-workers, and quote Thomson, Leighton, and Swartz (575), whose work points to vicarious functions or interchange of function, between the two kinds of tissue. The last-named authors found that the transplantation of a portion of the thyroid into the red bone-marrow in dogs prevents the tetany and allied symptoms which follow extirpation of all the parathyroids. On the other hand, Bircher (46) and Schneider (531) quite recently stated that the symptoms of post-operative tetany were relieved by treatment with parathyroid substance, while thyroid material was without effect.<sup>1</sup>

<sup>1</sup> Brown (*Annals of Surgery*, March, 1911) reports a case in which he removed the whole thyroid apparatus. Severe tetany ensued. After having tried all other methods without success, he finally cured his patient by grafting three parathyroids and a piece of thyroid from a corpse.

**U. The Relationship of Thyroids and Parathyroids to the Ductless and Other Glands, and in particular to the Pituitary Body.**

From the time when the ductless glands first began to be known there has been a decided tendency to regard them as more or less related to one another physiologically. Many of the suggestions which have been made were of an *a priori* character. Cyon (110) has put forward an elaborate theory as to the mutual functions of the thyroid and the pituitary body, and he regards the latter as a centre from which the vascular supply of the brain is influenced through the former. Sajous (519) apparently postulates a relationship between all the ductless glands, whose functions, according to this writer, dominate most of the bodily activities, normal and pathological.

Rogowitsch (499) stated that the pituitary acts vicariously for the thyroid, and that in rabbits and other animals which can survive the operation of thyroidectomy the functions of the thyroid are maintained by increased activity on the part of the pituitary body. Other observers [Gley (187), Pisenti and Viola (465), Schöneman (534)] have found changes in the pituitary body consequent on removal or disease of the thyroid.

Herring (237) has recently reinvestigated this subject, and finds that after thyroidectomy there is increased activity of the cells of the pars intermedia of the pituitary body. The most striking changes, however, are manifested in the nervous part of the posterior lobe and in the laminae forming the floor of the third ventricle. In these situations granular, hyaline, or colloid bodies become very numerous. They appear to be—in part, at least—of a cellular nature, and to find their way between the ependyma cells into the infundibular recess and ventricles of the brain. The colloid appears to arise from the epithelial cells of the pars intermedia.

Viguier (611) reports that in a lizard (*Uromastix acanthinurus*, Bell) he finds some modifications in the structure of the pituitary after thyroidectomy. But these, like the corresponding changes in the parathyroids (see p. 340), are incomplete and temporary.

It appears, further (576), that removal of the para-

thyroids produces compensatory changes in the pituitary body similar to those induced by removal of the thyroid, and this, if confirmed, will afford additional evidence of the intimate functional relationship subsisting between thyroid and parathyroid (see Fig. 84). It is suggested that thyroid, parathyroid, and pars intermedia of the pituitary form together an apparatus whose parts not only work together physiologically, but are closely related developmentally.

This relationship between the thyroid apparatus and the pituitary body is not admitted on all hands. Thus, Cimorini

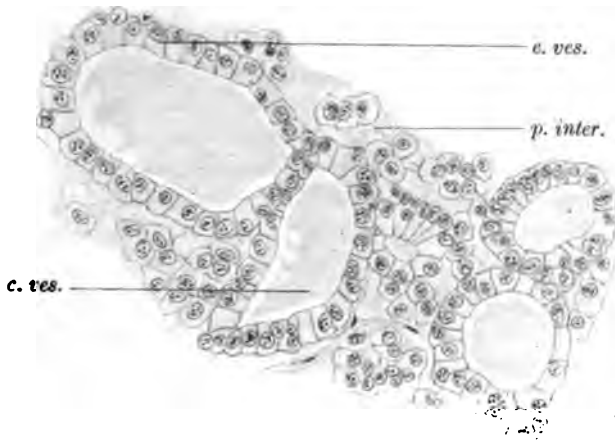


FIG. 84.—Small portion of the pars intermedia of the pituitary of a dog, which died some weeks after parathyroidectomy. The structure is practically indistinguishable from that of thyroid.

*c. ves.*, colloid vesicle; *e. ves.*, epithelium of colloid vesicles; *p. inter.*, pars intermedia of pituitary body.

(85) cannot find any changes in the pituitary after parathyroidectomy. Simpson and Hunter (555) report that complete removal of the thyroid gland in lambs does not lead to the appearance of iodine in the pituitary. On the assumption that the iodine-containing substance of the thyroid represents its active secretion, this does not support the Rogowitsch theory that in thyroid insufficiency the pituitary vicariously takes on its function. There was, however, some compensatory hypertrophy of the pituitary bodies.

Some questions of relationship between the thyroid and adrenal bodies have already been discussed (see p. 216).

During the present year some experimental evidence has been put forward which tends to show that the thyroid secretion acts as a stimulus to adrenal activity<sup>1</sup> [Hoskins (265)].

The statement of Falta and Rudinger (156) that adrenalin injection does not cause glycosuria in thyroidectomized animals cannot be corroborated by Grey and Santelle (203), nor by Underhill (589). Guleke (209), prompted by the work of Kostlivy (310), has carried out a series of experiments upon animals, in order to investigate the relationship between parathyroids and adrenals in regard to tetany. The results indicate that the parathyroid tetany may be relieved by extirpation of the adrenals. The relief of tetany after adrenal extirpation did not occur if some functioning thyroid were left behind. The author concludes that there is an antagonism not only between parathyroids and adrenals, but between parathyroids and thyroids.

A relationship between the thyroid and the reproductive organs has been postulated for a very long time. Specially has a connection between the thyroid and the female generative apparatus been recognized. The larger size of the thyroid gland in women was noticed by the early anatomists, and the periodical enlargement of the gland during menstruation and pregnancy has long been a matter of common knowledge. Some experiments are recorded which seem to indicate that the thyroid gland has some beneficial effect upon the course of normal pregnancy.

It has been stated that castration hinders the onset of parathyroid tetany in dogs and bitches [Silvestri (549)], but Massaglia (368) cannot confirm this.

There seems to be some relation between the thyroid and genital organs in bitches, as indicated by changes in the nitrogenous metabolism; but this, apparently, does not apply to the parathyroids [Rosenthal and Schwenk (505)].

#### V. The Internal Secretion of the Thyroid Apparatus.

It is commonly stated that the internal secretion of the thyroid gland passes, not directly into the blood-stream, but indirectly, by means of the lymphatic vessels. This requires a little discussion.

In the first place, it must be submitted that we have

<sup>1</sup> See also the reference to the work of Asher and Flack (12), (p. 349).

at the present time no certain evidence that the colloid of the thyroid vesicles is in itself, or contains, the active principle of the gland. As we have seen, also, the relation of the iodine to the colloid is doubtful [Claude and Blanchetière (87)].

The view, so commonly adopted, that the thyroid secretion is poured out by way of the lymphatics, appears to be founded upon the observations of Baber (14), Biondi (40), Langendorff (318, 319, 320), and Hürthle (269) that a substance apparently identical with the colloid within the vesicles may be found in the lymphatics outside them. Moreover, minute canals between the cells of the vesicles could be shown by injection.

Much of this work will not bear critical examination, and we must turn to some other method of investigation. The general character of lymph from goitrous glands seems to be the same as from cervical lymph generally.<sup>1</sup> Chemical tests for iodine in thyroid lymph were negative (the relation of iodine to the thyroid secretion is still an open question). The thyroid and parathyroids can perform their functions with or without colloid or iodine in the glands. "There is at present no adequate test for the thyroid-parathyroid secretions in the body fluids. When such tests are discovered, it will, in all probability, be found, in view of what is now known concerning the distribution and paths of absorption of all other internal secretions, that these secretions are more concentrated in the blood than in the lymph, and that they enter the blood directly rather than indirectly through the glands lymphatics" [Carlson and Woelfel (77)].

Until quite recently no attempt has been made to investigate the actual process of internal secretion by direct physiological means.

A very interesting series of experiments has recently been carried out by Asher and Flack (12). These authors have utilized the discovery of Cyon (110, 111) that the excitability of the depressor nerve is increased by the action of thyroid substance. They conclude that the thyroid furnishes an internal secretion which increases the excitability of the depressor nerve, and augments the effect of adrenin upon the blood-pressure.

<sup>1</sup> See, however, Asher u. Barbéras (11).

The thyroid furnishes this secretion under the influence of certain secretory nerves—viz., the superior, and to some extent, also, the inferior, laryngeal nerve. They arrive at these conclusions because they find in their experiments upon rabbits that stimulation of the depressor nerve and intravenous injection of adrenin produce more powerful results on the blood-pressure during stimulation of the thyroid nerves than previously without such stimulation.

They find, further, that extirpation of the thyroid abolishes this phenomenon, and that intravenous injection of thyroid substance produces the same effects as stimulation of the thyroid nerves. Thus, it follows that in extracts of the thyroid substance is contained the same active substance as is given out by the organ as an internal secretion.

Thyroidin is not capable of inducing similar effects. This and other new facts are evidence that thyroidin is not the physiological secretory product of the thyroid gland.

The increased rise of blood-pressure through adrenin is not observed unless the depressor nerves are cut. This, the authors think, is a regulatory mechanism, by which oppositely directed actions are suspended unless the necessity arises for one or other to preponderate.

The authors suggest that, as a consequence of these experimental results, Basedow's disease must be regarded as under nervous control. They further point out that their experiments indicate a close relationship between the thyroids and the adrenals, and also that morbus Basedowii is in part due to a disturbance of function of the adrenals, owing to an exaggerated stimulation of the sympathetically innervated tissues.

#### **W. Summary of the Chief Facts in regard to the Functions of the Thyroid and Parathyroid Glands.**

Several theories which have been advocated as to the functions of the thyroid and parathyroid glands have already been discussed in the previous pages. It remains to give a brief review of the various results arrived at as they present themselves to the present writer.

Although the majority of recent authors are inclined to look upon thyroids and parathyroids as totally separate and independent organs possessing distinct functions, it

must be submitted that this view is not warranted by the evidence before us. From the standpoint of comparative anatomy, there are many reasons for believing that there is an intimate relation between the two structures, and the experimental evidence as to a supreme vital importance of the parathyroids as distinct from the thyroids is unconvincing. Removal of thyroids only may sometimes give rise to nervous symptoms (tetany), while removal of parathyroids only may occasionally cause chronic symptoms (cachexia).

The frequent anatomical continuity of the two kinds of tissue and the existence of transition forms are very significant. And not less so is the occasional occurrence of colloid vesicles in the parathyroid glandule. The change of parathyroid under certain circumstances into a material which closely resembles thyroid, and the converse change of thyroid into a structure possessing many parathyroid features, must be taken to indicate a close anatomical and physiological relationship between the two. It seems probable that we have to look upon thyroid and parathyroid as constituting one apparatus, and probably the pars intermedia of the pituitary body may have to be added as a third constituent of the apparatus.

Removal of the thyroids and parathyroids gives rise to serious symptoms, and very frequently fatal results in some animals (dogs, cats, wolves, foxes), while in others (sheep) there may be very little ill-result. In still others (monkeys) there are chronic symptoms (cachexia and liability to various infections, with psychical depression) or acute symptoms (often transitory tetany), but the ill-effects frequently subside, and the animals may live a long time. It is difficult or impossible by artificial means to induce symptoms in all respects resembling myxœdema, so the conclusion is inevitable that the pathogeny of myxœdema must be more complex than simple thyroid insufficiency.

It is clear that the thyroids and parathyroids have a great importance in the economy of most animals. It is, further, quite clear that certain lesions of the glands give rise to symptoms which are due in part to absence of the proper functions of these glands. It has been proved that administration of thyroid substance relieves these symptoms in a very remarkable manner.



As in the case of the other ductless glands, many authors believe in an antitoxic function of the thyroid apparatus.

The most usually accepted theory is that the thyroid manufactures an internal secretion, which is essential to the proper growth and normal metabolic functions of the whole body. This may easily and reasonably be combined with the antitoxic theory. It may be supposed that the function of the internal secretion is to prevent poisoning by the products of body metabolism or by infections from without, and the extreme liability of thyroidectomized animals to various infective conditions is strong evidence in support of this view.

There is some evidence that the internal secretion of the thyroid gland is controlled by nervous impulses passing down to the organ by the superior (and to some extent, also, the inferior) laryngeal branches of the vagus nerve.

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.<sup>1</sup>

<sup>1</sup> 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.

Other recent papers on the general physiology and pathology of the thyroid apparatus are : Modler (400), Kottmann (311), Léopold-Lévy and de Rothschild (332). On the surgery of the apparatus the following may be noted : Palla (446), Oberst (432), Sudeck (566).

Professor Asher informs me that he has recently had the opportunity of testing the physiological action of fluid drawn off from a human thyroid. It was found to increase in a marked degree the irritability of the vagus nerve.

## CHAPTER XIV

### THE FUNCTION OF THE THYMUS

#### A. Comparative Anatomy and Development of the Thymus.

1. NOTHING is certainly known of the thymus in the Cyclostomata.

In Elasmobranchs the thymus arises on each side as epithelial outgrowths of the dorsal gill-pockets (Dohrn). The number of clefts which give rise to thymus elements varies in different species, but it is probable that thymus buds originally arose from all the clefts.<sup>1</sup>

A similar origin may be assigned to the thymus in Dipnoi, Ganoids, and Teleosts; but in these groups modifications occur in the directions of resorption and fusion of originally separate portions [Wiedersheim (73), Hammar (17, 18)]. In Teleosts the separate rudiments unite into a single mass which, in contrast with the course of events in Elasmobranchs, remain in connection with the gill epithelium. Growth is generally in a backward direction dorsal to the branchial arches, but the position varies in different species.

2. In Urodela the thymus arises in the form of compact outgrowths from the epithelium of the dorsal gill-pockets from 1 to 5.

In the Anura the organ arises exclusively from the second cleft.

In adult Amphibians the thymus lies behind and above the mandibular articulation. In the frog the gland is found behind the annulus tympanicus, covered by the depressor mandibulæ muscle. It is a small, longish, oval body, which may be 2 to 3 millimetres in length.

3. The thymus of reptiles has been specially investi-

<sup>1</sup> See Fritsche (13).

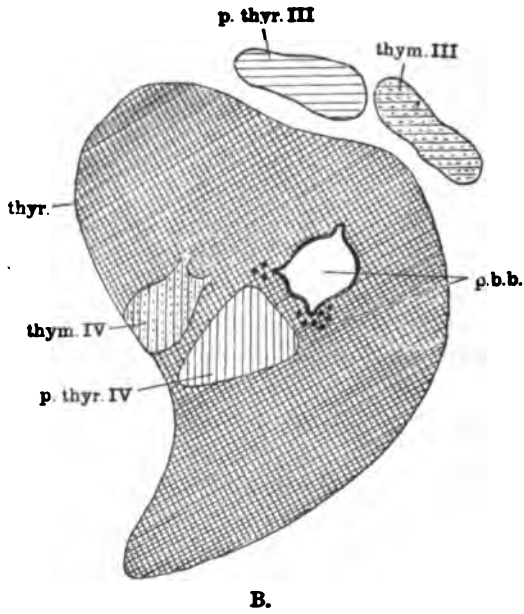
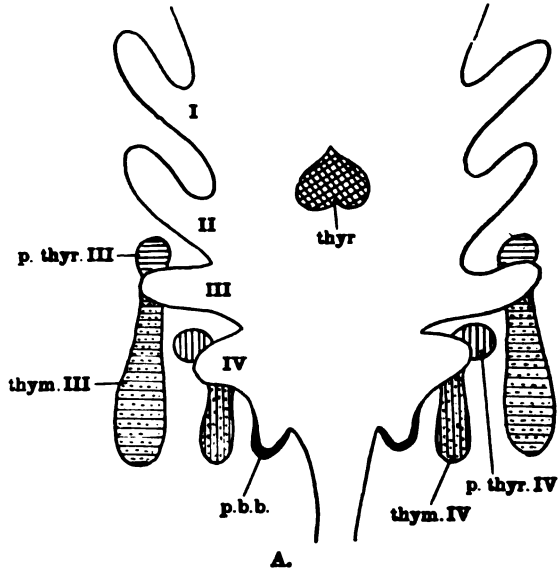


FIG. 85.

gated by de Meuron [Thyroid literature (392, 393)], Van Bemmelen [Thyroid literature (30, 32, 33)], and Maurer [Thyroid literature (374, 375, 376)]. The organ arises, as in the lower groups of vertebrates, from the dorsal gill-pockets, in the lizard from II. and III., in snakes from IV. and V.

4. In birds, thymus buds have been described from third, fourth, and fifth clefts.

5. The thymus of mammals apparently differs very materially in many respects from that of all lower animals, inasmuch as it is much more complex, and it is not the dorsal, but the ventral, pockets of the gill-clefts which furnish its rudiment. In most cases the third cleft is the most important, but sometimes the fourth, and occasionally, also, the second, plays a part. This portion of the origin of the gland is entodermal (see Fig. 85).

Recent work [Zotterman (76)] has confirmed the observations of Kastschenko (28) as to the occurrence of an ectodermal component, derived from the "ductus præ-cervicalis," in the thymus of certain mammals. This con-

EXPLANATION OF FIG. 85.

(Diagrams A and B).

A illustrates the development of the branchial organs of mammals, B shows their actual relations in the adult.

The different related rudiments of the same branchiomere are represented by a similar direction of shading lines; so also the corresponding organs. Thus the rudiments from the third cleft are represented in A by horizontal lines, as also the organs thus arising in B. The rudiments and organs from the fourth cleft are characterized by vertical lines. The post-branchial body is shown in thick outline, the thyroid by crossed lines.

The different kinds of tissue arising from one and the same branchiomere are indicated by differences in the shading. The parathyroid tissue is shown by lines, the thymus tissue by alternate continuous and interrupted lines. The post-branchial body is represented in the developed condition as a hollow space with several glandular nodules (shown in dark circles).

A shows the four internal gill slits (I. to IV.), the epithelial origins of the parathyroids (*p. thy.* III., *p. thy.* IV.), the origin of the thymus (*thym.* III., *thym.* IV.), the rudiment of the thyroid (*thy.*), and that of the post-branchial body (*p.b.b.*).

B represents a schematic transverse section through the fully developed thyroid (at about the level of the junction of the upper and middle third of the thyroid lobe of a cat). The lettering corresponds to that in Diagram A. The structures which arise from the third cleft become the "external" parathyroid and thymus nodule (separated fragment of thymus III.); those which arise from the fourth cleft become the "internal" parathyroid and the thymus nodule (*p. thy.* IV., and *thym.* IV.). The post-branchial body is surrounded by thyroid tissue.

[A is after Groschuff (204) in ruminants; B from Kohn (309) in the cat.]

ception must have a far-reaching effect upon our views as to the origin and nature of the mammalian thymus. From a phylogenetic standpoint the ectodermal and the entodermal thymus representatives must be regarded as two distinct organs, which, through a parallelism in development, have acquired a similar structure.

There are three types of thymus in mammals :

1. A purely entodermal thymus. This is found in the human subject [Hammar (21)] and in the rabbit [Hanson (22)].

2. A purely ectodermal thymus. This is found in the mole.

3. A mixed entodermal and ectodermal thymus. This condition is found in the pig [Zotterman (76)] and the guinea-pig [Ruben (21A)].

While in crocodiles and birds the thymus is situated in the neck, in mammals it is for the most part situated in the thorax. But in some mammals there is a cervical portion as well as a thoracic portion, while, again, in some species, such as the guinea-pig, the structure is entirely cervical. How far the distinction between an entodermal and an ectodermal thymus corresponds to the cervical and thoracic representatives of the gland is not known. But it is stated [Anikiew (3)] that the cervical thymus of the guinea-pig is entirely entodermal, being derived from the third cleft, and corresponds to the human gland, which, however, is thoracic.

This acceptance of a dual origin of the mammalian thymus will necessitate a reinvestigation of the development of the organ throughout vertebrates. But it must be borne in mind that a definite statement as to whether a derivative of a gill-cleft is ectodermal or entodermal in origin is often a matter of extreme difficulty.

The human thymus is derived from the third visceral pouch, but it is not yet decided as to whether there is an accessory rudiment from the fourth pouch. The thymus is thus in its first origin bilateral. A pocket develops from the third cleft on each side, and extends itself as a thick-walled tubular prolongation along the carotid artery. The pocket persists as the "thymus vesicle" in the proximal section of each rudiment. From the lower end of the tube

solid epithelial buds are given off, and from these lateral buds again come off, so that this part of the gland acquires a ramified lobular appearance like an acinous gland. The acini, however, are solid. The two rudiments are brought into close contact with one another in front of the trachea, and unite to form a single-lobed body, which comes to lie in the anterior mediastinum in close relationship with the pericardium.<sup>1</sup>

### B. Structure of the Thymus.

The thymus is made up of several lobules, which vary in size, and are separated from one another by connective-tissue septa, bearing bloodvessels and lymphatics.

Each lobule may be divided into a cortical and a medullary portion. The cortex is incompletely separated into "nodules" by connective-tissue trabeculæ, the arrangement bearing a strong resemblance to that of a lymphatic gland. The cortex is very vascular, and is similar in appearance to a lymphatic gland. Its structure also agrees with that of lymph glands and tonsils in exhibiting numerous signs of mitosis, but without definite germ centres. In addition to the lymph cells, there are also a number of peculiar granular cells.

The medulla, like that of a lymphatic gland, is more open in its texture than the cortex, and its reticulum is made up of large, transparent, branched cells, which are sometimes arranged in an epithelioid manner. The medulla does not contain so many leucocytes as the cortex, but is characterized by the presence of the peculiar concentrically striated bodies—the concentric corpuscles of Hassall. These vary very considerably in general appearance, and their precise origin and significance are still matters for discussion.

The above account is largely derived from that given by Schäfer in a recent textbook. It seems possible that there are many points in connection with the thymus upon which current views may have to be changed. It has long been taught that the human thymus reaches its greatest development at about the second year, and then begins to degenerate. But it was shown in the year 1890 by Waldeyer

<sup>1</sup> For an account of the literature of the development of the thymus the reader is referred to Maurer (35).

(67, 68) that even in advanced age a considerable amount of thymus tissue persists, and probably maintains its function. Zoja (74, 75) had previously shown that the thymus frequently persists till the age of puberty. Recently Hammar (17) has insisted that the organ continues to grow up to the period of puberty, and reaches its greatest development between the fourteenth and sixteenth years. From that time onwards it gradually loses in weight, but microscopical investigation shows that it still functions.

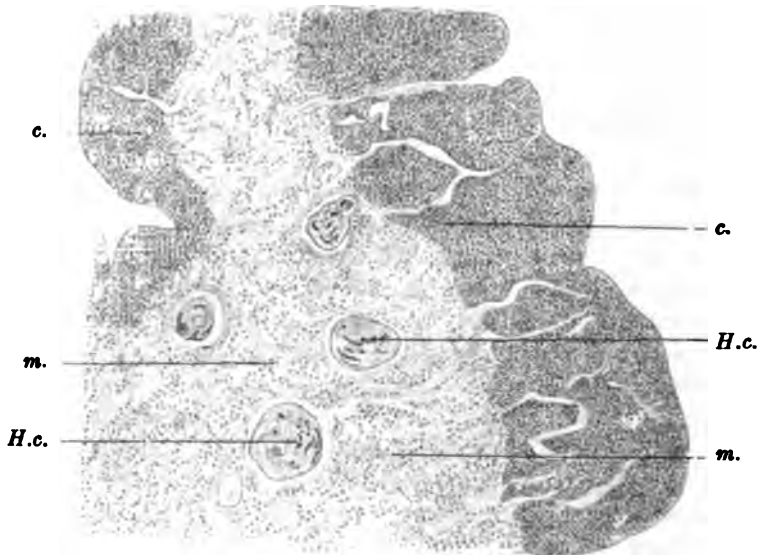


FIG. 86.—Portion of the thymus gland of a monkey, as seen under a low power of the microscope. (Drawn by Mrs. Thompson.)

*c.*, cortex ; *H.c.*, Hassall's concentric corpuscles ; *m.*, medulla.

A true atrophy of the parenchyma, with elimination of function, comes on at about fifty to sixty years of age.

It seems, then, that we must regard the thymus as an organ regularly present, and probably in an active functional condition up to the age of puberty. The explanation offered by Hammar of the opposite conclusion reached by former anatomists is this: Wharton in the seventeenth century observed that a reduction in size of the thymus frequently occurred in exhausting or wasting diseases. This has been frequently noted, and so it has been customary to look upon

the thymus as a kind of "barometer" to indicate the state of nutrition. But more often the mistake has been made of confusing this "accidental involution" with the age involution.

It seems somewhat doubtful whether we are to look upon the thymus in its fully developed condition as a lymphoid organ. According to Wiedersheim (73), "Jedenfalls stellt die thymus zu keiner zeit ein 'lymphoides Organ' dar." Hammar (17, 18) has brought forward evidence that, not only in its origin, but throughout life, the thymus has the characters of an epithelial organ. But there are undoubtedly leucocytes present, and Hammar believes, as did the older observers, that these are of mesodermal origin, invading the gland secondarily, and there undergoing further proliferation.

Stöhr (57, 58) believes in the epithelial origin and nature of the small thymic cells. These arise *in situ* from the repeated multiplication of the reticular epithelium, and though morphologically they come to assume a structure indistinguishable from that of the true lymphocytes, they remain throughout true epithelial elements.

We have, then, four prevailing theories as to the nature of the thymus element: (1) That the original epithelial elements are entirely replaced by a leucocytal invasion from the mesoderm, and that the thymus in its fully developed condition is a lymphoid organ; (2) that the original epithelial elements give rise to lymphoid cells *in situ*, and that the thymus becomes a lymphoid organ; (3) that the thymus remains an epithelial organ, but that there are lymphoid elements which have invaded it; (4) that there are no true lymphoid elements, but that the small thymic cells, which appear to be of a lymphoid nature, are, in reality, epithelial. This last is the view of Pappenheimer (43).

If this last view be correct, we should expect to find some differences between these cells and lymphoid elements. The present writer has given some little attention to the structure of the thymus (apart from embryological considerations), and it would seem that many of the thymus cells are indistinguishable from the lymphoid cells. But the matter is still in a very doubtful state, and needs



further investigation. The question is not only of morphological, but also of considerable physiological, importance. If the thymus cells are in truth epithelial throughout the life of the organ, we may with reason look for an internal secretion in the sense in which we defined it in an earlier chapter. On the other hand, if the cells be finally included among lymphoid elements, then we shall expect to find that the functions of the thymus are allied to, if not identical with, those of lymphatic glands.<sup>1</sup>

Hammar's most recent view (20) is that the thymus is an epithelial organ with a leucocytal infiltration. Hassall's corpuscles represent a functional differentiation of the epithelium. Under the influence of certain common disturbances, the thymus may undergo an "accidental involution" of a more or less transitory nature. Puberty normally brings on an "age involution," which is brought about by diminution of the leucocytal part of the organ, then by increased degenerative processes, by which the function of the organ and gradual destruction of the parenchyma are brought about.<sup>2</sup>

Pigache and Worms (49) report an "accidental involution" after thyroidectomy in dogs and rabbits; while Utterström (65) finds that feeding rabbits with thyroid substance has two distinct and opposing actions on the thymus, the one a depressor action due to the condition of reduced nutrition, the other a direct thymus excitation. This last action, according to Utterström, explains the enlargement of the thymus found in cases of exophthalmic goitre. Hoskins (26) notes that this hypertrophy of the thymus after thyroid feeding affects only the cortex.<sup>3</sup>

It has been proved [Hammar (17, 18), Bryce (6), Stöhr (58)] that leucocytes are already present in the body before the lymphoid transformation of the gland, so that the thymus

<sup>1</sup> It has not been considered necessary to give a full account of the history of the controversy as to the nature and origin of the thymus elements. The reader will find this in some of the papers already referred to, and also especially in the recent papers of Pappenheimer (43) and Maximow (36).

<sup>2</sup> The bursa fabricii of birds is an organ which in some respects may be regarded as analogous to the thymus. Thus it undergoes leucocytal invasion and a degeneration at about the age of puberty [Osawa (42), Jolly (27)].

<sup>3</sup> In the frog Mictens (38) looks upon the thymus as arising by the wandering in of leucocytes into an epithelial rudiment. Other recent papers on the histogenesis of the thymus are Dantschakoff (9) and Pigache et Worms (50).

cannot be the original source of the leucocytes, as suggested by Beard (4).

In regard to the Hassall concentric corpuscles modern investigation appears to show that these structures are not to be looked upon simply as remains of the original epithelium which have not become transformed into lymphocytes. Hammar (17, 18) and Bell (5) have shown that the concentric corpuscles are derived from hypertrophic reticular cells. The formation of these structures begins early in foetal life, and continues long into the period of post-natal evolution of the organ. Wallisch (69) has pointed out that the total volume of the Hassall bodies in young children exceeds that of the whole thymus in a three months' embryo.

It will not be possible to give a full account of the various thymus elements. One other thymic structure must, nevertheless, be briefly referred to. In 1888 Sigmund Mayer (37) described certain peculiar elements in the frog's thymus. These he regarded as rudimentary voluntary muscle fibres. Similar

structures were observed in Teleosts by Schaffer (54), who described them as sarcolytes in various stages of disintegration. Similar structures were discovered in birds and reptiles by Pensa (47). Mayer, Schaffer, and Pensa all considered them to be of a muscular origin and nature. Hammar (18), however, regards them as specially differentiated hypertrophic reticular cells, and therefore as closely related to the concentric corpuscles. Pappenheimer (43) has recently found these myoid cells in the human embryonic thymus, and holds the same view as Hammar as to their nature and origin.<sup>1</sup>



FIG. 87.—Hassall's concentric corpuscle from the thymus of a cat. This body shows a typical concentric arrangement. (Drawn by Mrs. Thompson.)

<sup>1</sup> Myoid cells have been described in the pineal gland of the ox by Dimitrowa (10), Nicolas (40), and Studnicka (60), and Pappenheimer (43) has found similar cells in a mixed tumour of the pineal gland in man. According to

### C. Extirpation of the Thymus.

Abelous and Billard (1) reported that the removal of both thymus glands in the frog always resulted fatally within three to fourteen days. Ver Eecke (11), however, pointed out that death did not occur if precautions against infection were taken by regularly renewing the water in the frog-tanks. The latter investigator was of opinion that removal of the thymus lowers the resistance of the frog to septic influences, and that this accounts for the fatality in the experiments of Abelous and Billard.

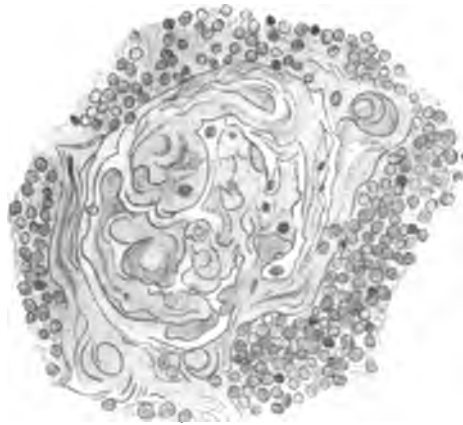


FIG. 88.—Hassall's concentric corpuscle from the human thymus gland. The concentric arrangement is not so regular or so marked as in the cat. (Drawn by Mrs. Thompson.)

The present writer (66) came to the conclusion that in the case of frogs extirpation of both thymus glands does not necessarily end fatally. Some of the animals experimented upon survived as long as thirty-six days, and have either been killed at the end of this time or have died of some cause independent of the operation.

Hammar (19) and Pari (44) have obtained similar results.

The earliest experiments upon mammals appear to be those of Friedleben (12). This observer operated upon twenty dogs and three goats; none of his animals died as the result of the thymus extirpation.

Tarulli and Lo Monaco (63) found that in dogs the thymus is not an indispensable organ. Only in very young animals had extirpation any results; there were in these cases disturbances of nutrition, diminution of muscular power, diminution in the number of the red blood-corpuscles.

Pappenheimer, they are identical in appearance with the myoid cells of the thymus, and their significance is equally obscure.

Toyofuku (64) finds occasional nodules of cartilage derived from the branchial arches in the thymus of the rat.

and of hæmoglobin, etc. These disturbances were only of short duration, and disappeared when the dogs grew older.

The present writer (66) could not ascertain that the removal of the thymus in guinea-pigs affects the animal in any way whatever. Litters of guinea-pigs of ages varying from ten days to a month were procured, and while some of the litter were submitted to operation, others were kept as controls. The young guinea-pigs appeared perfectly well an hour after the operation, and no symptoms of any kind supervened. They grew at the same rate as the controls, and no signs of changes in the blood were detected. Paton and Goodall (46) state that thymectomy induces a diminution in the number of leucocytes.

Within the last few years the thymus has received a great deal of attention, and a large amount of anatomical and physiological work has been carried out. The conception of the thymus as being not altogether a lymphoid organ seems to be gaining ground. A nutritive rôle has been suggested for the gland on account of the richness of the tissue in purin bodies. On the whole, the verdict seems to be that the organ is not essential to life, even in quite young animals [Weill (71)].

In young dogs it is stated that changes can be detected some months after extirpation of the thymus. The nutritive processes become defective, and none of the animals lived more than a year. On post-mortem examination, enormous dilatation of the heart was usually discovered. It is suggested that the thymus has an action antagonistic to that of the adrenal, so that, when the former is removed, there is a predominance of adrenal activity, and consequently hypertonus of bloodvessels and dilatation of the heart. Grafting additional thymus glands into young dogs caused serious disturbances to health [Hart and Nordmann (24), Nordmann (41)].

Klose (22), and Klose and Vogt (31), performed a series of extirpation experiments upon dogs between ten days and four weeks old. These authors divide the post-operative period into three stages: (1) A latent period, lasting from two to four weeks; (2) an adipose stage, which lasts two or three months; and (3) a cachectic stage, or the stage of "cachexia thymopriva" and "idiotia thymopriva." This

period extends to three to fourteen months. Death occurs with "coma thymicum," which often lasts a long time. The skeleton remains hypoplastic and dwarf-like, and the bones become atrophic. There is a deficiency of undissolved calcium. Bodily movements are feeble, and there are disturbances in the nervous system.

Interference with the growth, especially of the skeleton, is also described by Lucien and Parisot (33) and Paton (45).<sup>1</sup>

Changes in the pituitary and in the spleen after thymectomy have been recorded. Perrier (48) states that in the pituitary there is an increase of the chromophilic cells and a striking of cells of similar staining reaction. In the spleen there is an increase of the reticulum and a hypertrophy of the lymphoid tissue.

The thymus does not appear to have anything to do with the formation of red blood-corpuscles [L6w (32)], nor with the growth of epithelial organs [Andersen (2)].

Soli (55) states that extirpation of the thymus in adult hens causes them to lay eggs without shells. This is the only evidence which has been put forward up to the present time that the thymus has any function after the period of involution of the organ.

#### D. A Probable Relation between the Thymus and the Reproductive Organs.

Calzolari (7) in 1898 suggested a relationship between the thymus and the reproductive organs, and performed a series of experiments upon rabbits, with the object of putting the matter to the test. He found that in castrated male rabbits the volume and the absolute weight of the thymus were greater than in normal animals. He concludes that the thymus atrophies more slowly in animals from whom the testes have been removed.

Henderson (25) obtained similar results in rabbits, guinea-pigs, and cattle. He states, further, that in bulls and unspayed heifers the normal atrophy of the thymus which begins after the period of puberty is greatly accelerated when the bulls have been used for breeding, and when the heifers have been pregnant for several months. The re-

<sup>1</sup> See also Klose (30). According to Rachford (51), the thymus controls the lymphoid structures of the body generally.

tarded atrophy is due, according to Goodall (16), to a persistent growth of the lymphoid tissue, a delay of the fatty invasion, and a delay in the process of disintegration of the epithelium composing the Hassall's corpuscles.

According to Marrassini (34) and Gellin (15), castration gives rise to an enlargement of the thymus. Squadrini (56) believes that castration interferes with the normal involution of the gland. From these observations it would appear that the normal involution of the thymus is due to the development of the reproductive organs, though this cannot be the only cause. The experiments, further, tempt one to the hypothesis that the thymus furnishes an internal secretion of some kind which ministers to the needs of the economy before the reproductive organs are fully developed. Normally this internal secretion is provided by the testes (or ovary) after puberty, but if castration is performed, the thymus maintains its original structure and functions. This internal secretion must, of course, be of a different nature from that which determines the development of the secondary sexual characters, as these do not become manifest in castrated animals.

#### **E. Physiological Effects of Extracts of Thymus.**

Svehla (61) found that the thymus of the ox during embryonic life yields to extracts a substance which lowers the blood-pressure. This he considers as a manifestation of an internal secretion. From what has been said in an earlier chapter, it is clear that this depressor substance is simply that unknown material which is common to all animal tissues and organs. It is not specific for the thymus.

#### **F. Pathology of the Thymus.**

Perhaps the chief medical interest attaching to the thymus arises from certain remarkable cases of thymic death ("mors thymica"). In cases of thymic enlargement the essential symptom is a respiratory disturbance resulting from the diminution of space in the superior thoracic strait. This disturbance may vary from a mild stridor to a fatal dyspnoea. Sometimes the dyspnoea is of an asthmatic character ("thymic asthma").



“*Mors thymica*” is a term applied to those cases in which death occurs suddenly, without a definite history of previous respiratory difficulty. This may happen even when there are no other symptoms of the status lymphaticus, but very frequently this condition is present, and the thymus enlargement is associated with adenoids, and with enlarged tonsils and lymphatic glands.

The cause of death in these cases has been the subject of much discussion. It is probable that in the majority of instances the case is one of suffocation from tracheal stenosis and secondary laryngeal spasm [Warthin (70)]. At any rate, a detailed discussion of this subject is not likely to shed light on the function of the organ.

Some cases of Addison's disease appear to be combined with the status lymphaticus [v. Werdt (72)].

Gebele (14) describes persistent thymus in exophthalmic goitre.<sup>1</sup>

<sup>1</sup> Other recent papers on the pathology of the thymus are: Stoerk (59), Clark and Richardson (8), Symes (62), v. Neusser (39), Harbitz (23).

## CHAPTER XV

### THE FUNCTION OF THE PITUITARY BODY

#### A. Comparative Anatomy of the Pituitary Body.

##### 1. *The Mammalian Pituitary Body.*

RATHKE (137) was the first to point out the double origin of the pituitary body, from the brain and from an invagination of the mucous membrane of the alimentary tract. Other observers of this period looked upon the body as part of the brain. Luschka (102) called the body a "nerve gland," consisting of two parts, separated by pia mater; while Ecker (44) includes the structure of both portions under the name "Blutgefäßdrüsen."

Burdach (22) regarded the nervous portion as the "filum terminale anterius" of the cerebro-spinal canal; and Virchow (177) noticed in the anterior portion colloid vesicles like those of the thyroid. This has also been remarked by Rogowitsch (143), H. Stieda (167), and Schönemann (157).

The anterior lobe is admittedly glandular in its nature, but the structure of the posterior lobe has been variously described. W. Müller (119), Schwalbe (158), and Toldt (171) looked upon it as a mass of connective-tissue cells and fibres, which, during the course of development, have destroyed all trace of the original nerve tissue. Berkley (17) described nerve cells and glia cells in the posterior lobe. Kölliker (89) speaks very doubtfully about the matter, even about the results of investigation by the silver chromate matter.

Osborne and Swale Vincent (123) could detect only very few undoubtedly nerve cells in the infundibular portion.



These observers also confirmed and utilized experimentally the fact first observed by Peremeschko (130) that the posterior lobe has an epithelial investment.

The pituitary body consists of three portions: (1) The anterior lobe; (2) the intermediate portion; and (3) the posterior lobe, or nervous portion.

There are three types of mammalian pituitary body. In the first, of which the organ of the cat furnishes an example, the posterior lobe is hollow, and its cavity is in free communication with the third ventricle of the brain, and the epithelium of the anterior lobe almost completely surrounds the posterior lobe. In the second type (as, for example, in the dog) the body of the posterior lobe is solid, but the neck is hollow, and communicates with the third ventricle, and the posterior lobe is almost completely surrounded with epithelium, as in the first type. In the third type—*e.g.*, man, monkey, ox, pig, and rabbit—the body and neck of the posterior lobe are solid, although traces of a cavity are occasionally found in the neck. In this last type the epithelium of the anterior lobe does not spread so far round the posterior lobe, but is gathered around the neck and spreads over and into the adjacent surface of the brain [Herring (78)].

The epithelial portion is again divided into two parts: (1) An anterior lobe proper, consisting of solid columns of cells, between which run wide bloodvessels; and (2) an intermediate portion, which lies between the anterior lobe and the nervous portion, forming a close investment to the latter.

The anterior lobe presents all the appearances of a true internally secreting gland. Its structure is clearly that of a gland—an “epithelial body,” in Kohn’s phraseology (90). It is made up of a branching, compact network of epithelial threads and columns. In the spaces of the epithelial network run wide, thin-walled bloodvessels, so that in many cases the epithelial cells are placed directly on the delicate vessel wall. This arrangement is most admirably adapted for the purposes of internal secretion. The general scheme of structure is the same as in the adrenal cortex, the islets of Langerhans of the pancreas, the thyroid, and the thymus (in its epithelial stage).

The general nature of the cells found in the glandular pituitary may be thus stated :

1. Chromophile  $\left\{ \begin{array}{l} (\alpha) \text{ Acidophile.} \\ (\beta) \text{ Basophile.} \end{array} \right.$
2. Chromophobe.

Besides the colloid, it is probable that there are other secretory products.

In no other endocrine gland are the granular products of secretion so well seen as in the anterior lobe of the

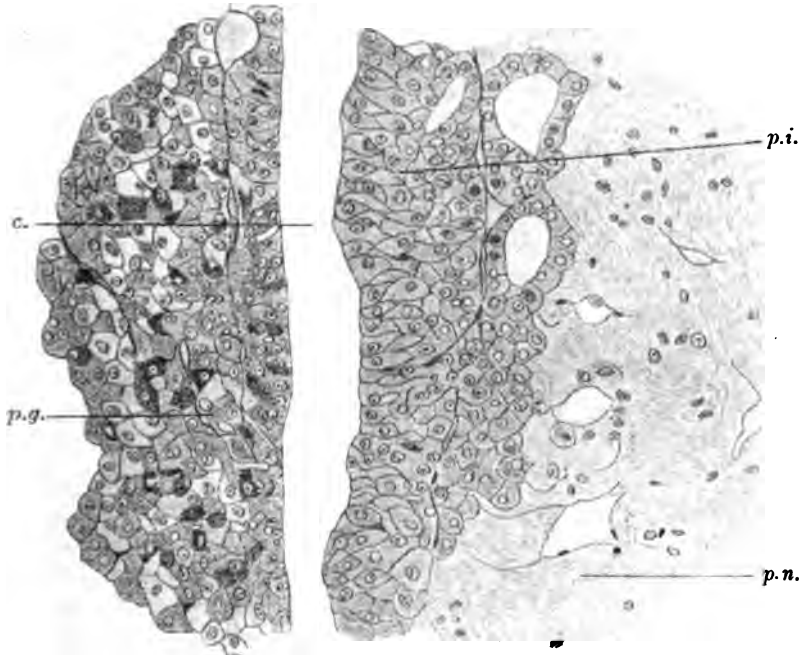


FIG. 89.—Section through a portion of the pituitary body of the dog, showing the glandular and nervous portions and the pars intermedia. (Drawn by Mrs. Thompson.)

*c.*, cleft in glandular portion (between glandular portion proper and the intermediate portion); *p.g.*, glandular portion; *p.i.*, intermediate portion; *p.n.*, nervous portion.

In the glandular portion are seen three kinds of cells.

pituitary body. Secretory granules are also seen in the vessels belonging to the gland.

A. S. and Helen Grünbaum (67), as a result of the examination of a large number of human pituitaries, come to

the conclusion that colloid material may be found in the bloodvessels, both in the anterior lobe and also in the so-called *pars intermedia*. Colloid material was not seen in the *pars nervosa*.

In children and in the foetus the distinction between the different varieties of cells in the anterior lobe is not marked, and colloid material is small in amount.

The size and weight of the gland and the amount of colloid material are subject to very great variation.

Cushing and Goetsch (36), as opposed to Grünbaum, find colloid masses in the posterior lobe of the pituitary, and agree with Herring that the colloid masses in this lobe are secretory products of the epithelial covering of the *pars intermedia*. They find in the cerebro-spinal fluid a substance which gives the same reactions as the *pars nervosa* itself.

The intermediate portion consists of finely granular cells arranged in layers of varying thickness closely applied to the body and neck of the posterior lobe and to the under-surface of adjacent parts of the brain. The part of it which is separated from the anterior lobe by the cleft is almost devoid of bloodvessels. Colloid material occurs between the cells of the *pars intermedia*.

The nervous portion is made up of neuroglia cells and fibres, and is invaded by the epithelial cells of the *pars intermedia*. A substance resembling the colloid of the thyroid gland occurs in the nervous portion. The glia cells are longish or cylindrical, with one, two, or more nuclei, and a granular, at times pigmented, cell protoplasm. From the protoplasm stretches a long, thin homogeneous fibre, which is sharply contoured, like an elastic fibre. These cells are young forms of ependyma cells—the “radial cells” of Retzius. In addition, there are “protoplasmic cells” which are multipolar, and send out fine glia fibres. There are also “spindle cells,” “giant glia cells,” “keratin cells,” etc. All these build up a primitive neuroglia.

One of the most interesting features of the posterior lobe is the pigment, which has been known for a long time. According to a recent careful account by Kohn (91), the pigment is contained within the threads of the neuroglia, and distends them here and there. When unstained, the substance is of a greenish-yellow tinge, and consists of

closely packed, irregular clumps. The amount of the pigment is found to become notably increased in age and disease. For this reason it is supposed to represent some kind of breakdown product. Livon and Peyron (98) think that the pigment bears some relation to the functions of the organ, and especially to the secretion of the anterior lobe.

Clunet and Jonnesco (31) have also given an account of the pigment in the neurohypophysis. According to these authors, the substance does not give the iron reaction. It is insoluble in alcohol, xylol, benzol, cedar oil, chloroform, and ether. It is stained red with osmic acid, red also with Sudan and Sharlach red, while it is blackened with iron hæmatoxylin.

The above account is largely taken from Herring (77, 78). A good account of the mammalian pituitary, with a complete literature, has recently been given by Trautmann (172).

For information on the dimensions and weight of the pituitary, see Livon (97).

Haberfeld (68) finds in the human subject at all ages a "pharyngeal pituitary"—a solid string of cells about 5 millimetres long, which runs from below upwards and backwards immediately behind the vomer. It contains cells like those in the pituitary itself, but here the chromophobe predominate, and the basophiles may be absent.

Pende (128, 129) also gives an account of this structure. He states that histologically it resembles the pars intermedia. It is the origin of most of the pituitary tumours [see also Citelli (29)]. This structure is probably the remains of the original pituitary duct. Arena (2) states that the structure of the pharyngeal pituitary is different from that of the ordinary glandular. He thinks that it is "rudimentary," and not of any great importance.

Haberfeld (69) describes a cystic structure in intra-uterine life, which is made up of glia cells and fibres, and possessing lumina, surrounded by ependyma cells. This body is frequently, he alleges, the starting-point of gliosarcomata.

Staderini (162) gives an account of the "eminencia saccularis" (an elevation on the base of the brain immediately behind the stalk of the pituitary). He considers

that the structure is not homologous with the "succus vasculosus" of fishes, as Retzius thought.

A very rare abnormality which has been described in connection with the sphenoid bone is a persistent, perforating foramen in the basisphenoid—the canalis cranio-pharyngeus [Landzert (95), Romiti (144)]. This is regarded as the place of exit of the original duct of the anterior lobe of the pituitary body. According to Spee (160), the foramen is typically found in the rabbit.

Haberfeld (70) finds the canal wanting in all acromegalic skulls in the Vienna Pathological Institute. He reports that it is very variable in individuals of the same species of animals. He calls attention to the fact that the pharyngeal pituitary is constant in man, while it is frequently absent in the lower animals. This is not what would be expected if the structure really represents the remains of the original duct of the pituitary.

### *2. The Pituitary Body of Birds and Lower Vertebrates.*

In birds the epithelial cleft appears to be absent [Herring (77)]. The cells of the anterior lobe are for the most part small and finely granular.

The posterior lobe is small and hollow, and much convoluted. Colloid bodies are sometimes present. The cells of the pars intermedia come into close contact with the nervous portion of the posterior lobe, but are gathered together for the most part in the neighbourhood of its neck and on the thin lamina of nervous tissue forming the floor of the third ventricle [Herring (77); see also Haller (72), Sterzi (166), and Gentes (62)].

In Teleostean fishes the posterior lobe has a complex vascular structure of a glandular nature, which was called the "saccus vasculosus" by Göttsche (66). L. Stieda (168) showed that the saccus vasculosus communicates with the brain cavity, and Rabl-Rückhard (135) named it an "infundibular gland" [see also Kupffer (94)].

The Teleostean pituitary is composed of three kinds of tissue, two of which are epithelial and the third nervous, the latter being comparatively small in amount. The anterior lobe of mammals is represented by a wedge-shaped mass of large and deeply staining cells. These cells vary

in situation and extent in different species [Sterzi (166), Gentes (62), Herring (77)]. The pars intermedia consists of small, round, feebly staining cells, which surround and invade the nervous tissue. The pars intermedia in the cod is divided into two main portions, which are continuous with, and separated from one another by, the true anterior lobe [Herring (77)].

The nervous part of the cod's pituitary is small, and appears to be composed of neuroglia and ependyma cells, without any true nerve cells. It is continuous with the brain in front by the lamina post-optica, or anterior lamina, and at the sides by lateral laminae. The nervous substance is more freely invaded by cells of the pars intermedia than is the nervous substance of the mammalian body.

In Elasmobranchs (*Raja batis*) the pituitary is a long, club-shaped body which lies for the most part behind the small lobi inferiores. Its structure is very different from that of mammals, birds, and Teleosts. There are no cells having the deeply staining characteristic of those of the anterior lobe of other vertebrates, and there are no cells exactly like those of the pars intermedia. There is no differentiation into anterior and posterior lobes, and the only trace of a posterior lobe is a thin lamina of nervous tissue which bounds the infundibular cavity. The sacculus vasculosus is well developed. The Elasmobranch pituitary appears to be quite different from that of other vertebrates.

#### B. Development of the Pituitary Body.

The earlier observers believed that the whole of the pituitary body is derived from the brain. Rathke (137), however, described the invagination of mucous membrane, since called "Rathke's pouch," and put forward the view that from this pouch is derived the epithelial portion of the pituitary (which he further stated has been derived from the entoderm of the fore-gut. Reichert (140) stated that the epithelial pituitary is mesoblastic, and arises from the anterior end of the notochord. So, also, His (81). Both Rathke (138) and Reichert (141) later changed their opinions, and Reichert supposed that the anterior lobe arises from the cells of the pia mater.

Dursy (43) described the origin of the epithelial part from

the fore-gut, and of the vascular stroma from the notochord. W. Müller (119) showed that the anterior lobe arises from Rathke's pouch, but believed this to be entodermal. After the work of Götte (64) and Balfour (8), it has usually been considered that the pouch is of ectodermic origin.

The posterior lobe was originally conceived as the anterior extremity of the brain [v. Baer (7)]; but the researches of Götte (64), Mihalkovics (113), v. Wijhe (178), and Kupffer (94), have shown that it is an outgrowth of the thalamen-cephalon.

Mihalkovics (113) has given a complete account of the early development of the pituitary body in the rabbit and the chick. According to this author, the anterior lobe is developed from Rathke's pouch, and is ectodermal. The beginning of the pouch is in front of the oral plate. When this ruptures, its upper stump, containing in its upper part the head of the notochord, bends forward and narrows the mouth of the epithelial pouch, leading to the formation of a definite sac—the hypophysial sac. The wall of the sac presses upon the base of the anterior brain vesicle, giving rise at its upper extremity to a fold in the wall of the brain, which becomes the primitive infundibulum. The primitive infundibular process comprises the surrounding tissue of the tuber cinereum as well as the origin of the infundibulum, and the true infundibulum is formed at a later stage by its own growth from a portion of the primitive infundibular process. The head of the notochord, beyond presenting a barrier to the backward growth of the sac, takes no part in the formation of the pituitary body.

Mihalkovic's work has been confirmed in the main by Kölliker (88), Kraushaar (93), Minot (114), Kupffer (94), Salzer (147), and others. Kupffer described an additional origin of part of the anterior lobe of the pituitary from the entoderm of the fore-gut, and this view has received support from the observations of J. Nusbaum (121) and Saint-Remy. Herring (76), however, believes that the epithelial portion of the pituitary is entirely ectodermic. The account of the last-named author is briefly as follows :

Development of the pituitary body begins very early in embryonic life. In mammals the epithelial portion is derived entirely from the ectodermic wall of the buccal

invagination known as "Rathke's pouch." Its origin is single and mesial. The epithelium is early distinguishable into two parts. One of these—the intermediate part—is closely adherent to the wall of the cerebral vesicle; the cells are clear, and tend to form colloid. The other portion of the buccal epithelium gives rise to the anterior lobe proper. Its cells are granular, and form solid columns separated by blood-channels.

The infundibulum is an invagination of part of the wall of the thalamencephalon, which is adherent to the anterior and upper wall of Rathke's pouch. It therefore possesses an epithelial covering derived from the latter. The infundibular process grows backwards, and, in the cat, retains its central cavity. It is lined by ependyma cells, which, during development, become elongated, so that ependyma fibres run obliquely in its neck. The posterior lobe of the pituitary is, from the first, a composite structure of epithelium of the pars intermedia and of neuroglia and ependyma, and the relations between the two tissues become more and more intimate.

The early stages of development of the Elasmobranch pituitary resemble those in the mammal, except that there is no invagination of the wall of the cerebral vesicle in Elasmobranchs to form an infundibular lobe. The body is derived entirely from the buccal epithelium of Rathke's pouch.

The relation of the pituitary to the brain ventricles is similar to that in higher vertebrates, but this is accounted for by the development of a paired saccus vasculosus, each of which pours its secretion into a common infundibular canal. The wall of this is lined with epithelium similar to that lining the saccus vasculosus. Its nervous structure is lost, being replaced by connective tissue and numerous thin-walled bloodvessels. There is no invasion of the wall of the canal by epithelial cells, and no hyaline bodies are formed.

The pituitary body of the Elasmobranch is a gland, the secretion of which is poured directly into the bloodvessels. There is no evidence of any direct secretion by the pituitary into the brain ventricles [Herring (79)].



### C. Physiological Action of Extracts of the Pituitary Body.

Oliver and Schäfer (122) discovered that aqueous or saline extracts of the pituitary body produce, when injected into the bloodvessels, a rise of blood-pressure, which is comparable to that produced by extracts of the adrenals. The rise is produced by an action on the peripheral arterioles, as is that brought about by adrenal extracts. The action of pituitary extracts, however, is more prolonged than that of adrenal extracts. Oliver and Schäfer did not in these experiments obtain any marked effect upon the rate of the heart-beat. Nor did they differentiate between the action of the different parts of the gland, since they used extracts of the whole pituitary body.

Howell (85) made a considerable step in advance. He divided the gland into its two chief portions—the anterior and posterior lobes—and determined that, while an extract of the former is devoid of physiological activity when injected into a vein, that of the latter produces the effects upon the blood-pressure described by Oliver and Schäfer. Howell further found the rise of blood-pressure to be accompanied by a slowing of the action of the heart, and that both the raised blood-pressure and slow cardiac rhythm might be maintained for a considerable time; and that if a second dose be administered intravenously within a certain time—which varies from half an hour to an hour or more—after the first dose, these effects are not repeated—in other words, a certain immunity is established, which only slowly passes off.

Szymonowicz (169) obtained an effect with pituitary extract in two experiments only, and this he states was a slight lowering of the blood-pressure and a quickening of the heart-beat. These effects are quite different from those described by all other observers.

Cyon (38) has noticed, as did Howell, that the rise of blood-pressure is accompanied by slowing of the pulse. Both these effects he attributes to stimulation of the pituitary body by the extract which has been injected [Cyon (37)]. He states that stimulation of the hypophysis in the body, either electrically or mechanically, will produce similar results through the vagi, and that after extirpation of the organ the effects can no longer be produced by

injections. Biedl and Reiner (18), and also Schäfer and Swale Vincent (see below), were of opinion that the results obtained by intravenous injections of pituitary extracts point to an explanation different from that offered by Cyon.

Cleghorn (30) has obtained slowing of the isolated mammalian heart on perfusion of the "infundibular" extract.

Professor Schäfer, working in conjunction with the present writer (152, 153), found that the cardiac slowing

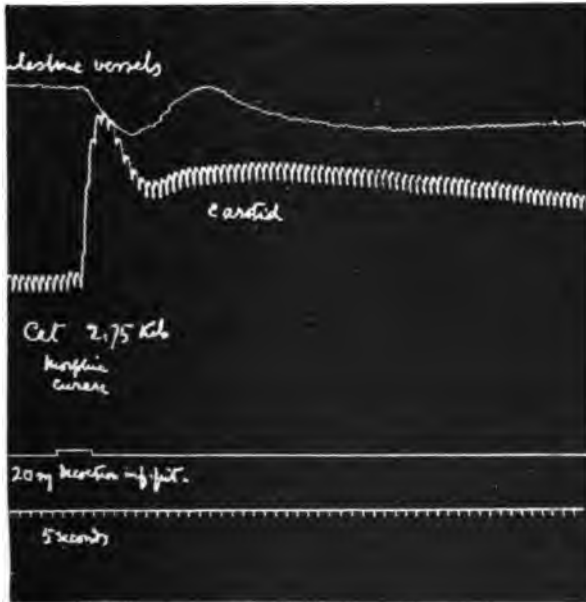


FIG. 90.—Effect upon the arterial pressure and intestinal volume of intravenous injection of decoction of infundibular body. Cat under morphia and curare. The time marking indicates five seconds.

described by Howell is not constant, and that, when present, it is not abolished by section of the vagi or the action of atropin. It is, therefore, of peripheral origin, and not due to the same cause as the inhibition which often accompanies the action of adrenin, which is brought about by an action upon the cardio-inhibitory mechanism in the bulb. Not only is there generally no *rise* of blood-pressure resulting from a second or third dose of the extract of posterior lobe, but there is *invariably a fall*, which, however, lasts only a short time. It was shown that this fall of

blood-pressure is due to a depressor substance acting upon the bloodvessels ; that the substance is soluble in alcohol, in which the pressor substance is insoluble ; and that it is not choline. Schäfer and Vincent employed ox pituitaries, and tested the action upon cats.

Osborne, in conjunction with the present writer (123), worked with ox pituitaries, but employed dogs and rabbits for purposes of experiment. The results were in the main confirmatory of those obtained by Oliver and Schäfer, Howell, and Schäfer and Swale Vincent ; but there is one difference, which appears to be due to idiosyncrasy on the

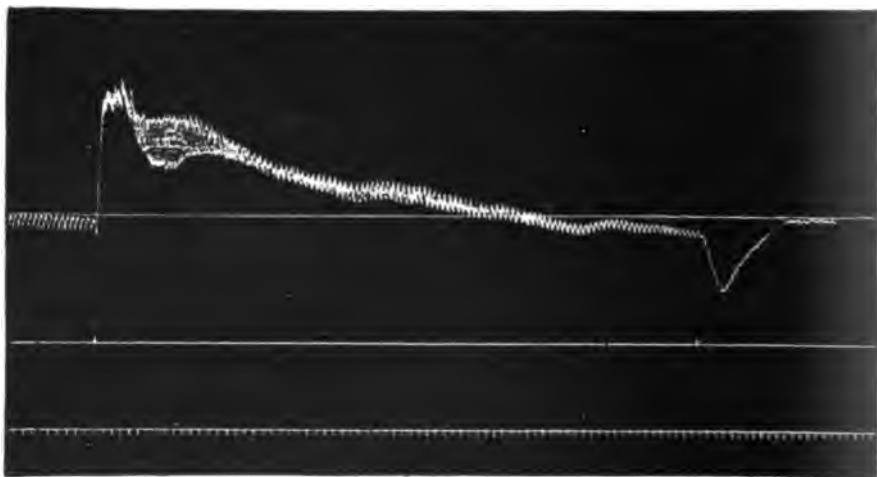


FIG. 91.—Effect upon the arterial pressure of intravenous injection of decoction of infundibular body. Cat. Morphia and curare.

part of the animals employed for experiment. The fall of pressure on repeating the injection is not mentioned by Howell, although he obtained almost constantly in the dog a preliminary fall as the result of the first injection. Schäfer and Vincent did not find this in their experiments, which were nearly all performed upon the cat. Osborne and Vincent frequently observed the preliminary fall in dogs described by Howell, but also in most cases obtained a pure fall on a subsequent injection. They found that the depressor substance is soluble in ether.

These facts, now corroborated by many experimenters, have been found to hold good also for the human pituitary

[Halliburton, Candler, and Sikes (73)], the posterior lobe of which alone exhibits the characteristic effects on blood-pressure.

But besides the pressor and depressor constituents of extract of the infundibular part of the pituitary body, this organ yields a substance soluble in water, and not destroyed by boiling, which acts specifically upon the kidney, producing, along with dilatation of the renal vessels, an increase of secretion from the tubules, and even causing a flow if the secretion, from the operative procedures or the anæsthetic, happen to be suppressed. The effect obtained from intravenous injection of only 1 c.c. of a 1 per cent. extract of the dried glandular substance may be as marked as that of such an actively diuretic substance as caffeine citrate. But the one or two grains of caffeine citrate which are required to produce active diuresis represent a vastly greater amount of material than that of the diuretic constituent in 1 c.c. of a 1 per cent. extract of the gland. The diuretic activity of the substance formed by and contained within the gland must therefore be far greater than that of any diuretic in the Pharmacopœia. Assuming that the pituitary is an internally secreting gland, these results render it probable that the main purpose of its secretion is ancillary to the function of the kidneys. The effect of its extract, both upon the vascular system generally and upon the renal vascular system in particular, is to produce those conditions which are most favourable to renal activity [Magnus and Schäfer (103), Schäfer and Herring (151)].

Schäfer and Mackenzie<sup>1</sup> have recently confirmed the statement of Ott that pituitary infundibulum is a rapid and powerful galactogogue. The galactogogue principle is contained in the pars intermedia and the pars nervosa. Corpus luteum extract has a similar effect.

Pituitary extract has also been found to stimulate other forms of involuntary muscle besides that of the arteries, and among these the pupil and the uterus may be specially mentioned.<sup>2</sup> The fact that infundibular extract causes uterine contractions was first recorded by Dale (39), and

<sup>1</sup> Proc. Roy. Soc., B. 568, 1911, p. 16.

<sup>2</sup> Cramer (*Quart. Journ. Exp. Physiol.*, i., 1908) finds that extracts of the posterior lobe of the pituitary body of the ox produce a distinct dilatation of the pupil of the enucleated frog's eye.

that powerful peristaltic movements of the intestines were set up was noted by Bell and Hick (11).

Frankl-Hochwart and Fröhlich (56) have recently investigated the effects of "pituirín" upon the sympathetic and autonomic nervous systems. In dogs and rabbits the injection induces contraction of the bladder, and raises the faradic irritability of the pelvic nerve—that is, of the vesical autonomic fibres—while the irritability of the hypogastric nerve—that is, of the vesical sympathetic fibres—remains unaltered. Similarly, the uterus of a rabbit during pregnancy or lactation undergoes a long-continued contraction and an increase in the irritability of the uterine sympathetic nerves.

On the other sympathetically or autonomically innervated organs pituirín has no action. For example, it has no effect on the cardiac fibres of the vagus, the chorda tympani, or the cervical sympathetic. Also, the irritability of the *nervi erigentes* in the dog remains unaltered. The author strongly recommends the drug for use in the case of the human subject.

Bayer and Peter (9), in studying the action of pituirín upon the isolated intestine, report that the substance produces first a diminution of the normal rhythmical contractions, with diminished tonus, followed by the opposite conditions.

It is stated that pituirín raises the blood-pressure to a greater extent in pathological conditions when the pressure is low than under normal circumstances [Klotz (86, 87)].

When administered regularly over a long period, extracts of the hinder lobe of the pituitary body give rise to wasting of the animal and degenerative changes in the liver and spleen. Extracts of the anterior lobe are inactive, except in animals with defective secretion of the gland. In these injection causes a temporary pyrexia [Cushing (35); see also Crowe, Cushing, etc. (33)].

These observations have led to the introduction of the extract as a therapeutic agent, as, for example, in producing uterine contraction after delivery [Bell (10)].

Schäfer and Herring attribute the actions of the extract to separate hormones, one acting on the muscular, another on the kidney tissues; but Dale (40) is inclined to the view

that it is not necessary to suppose that more than one chemical stimulus is at work.

Subcutaneous injection of the extracts in small mammals causes paralytic symptoms similar to those obtained by injecting adrenal extracts [Schäfer and Swale Vincent (152), and also Swale Vincent (176)].

**D. The Question as to which Elements of the Pituitary furnish the Active Substance or Substances.**

As we have already seen, Howell (85) discovered that it is from the posterior lobe only that active extracts can be obtained. This was confirmed by Schäfer and Vincent (152, 153). This observation was contrary to what might have been expected, since, from the distinctly glandular nature of the anterior lobe, it would appear *a priori* that it would be the more likely to furnish active physiological substances.

But, as we have seen, there are epithelial elements in, and in close relation to, the nervous portion, and it was a natural assumption that these, and not the nervous portion proper, would be found to yield the pressor substance. But Osborne and Vincent (123) tested the matter, and found that an extract made from the central part of the infundibular portion—devoid of epithelial elements—is much more active than one from the peripheral. They expressed their opinion that probably the external layer could be found to be inactive if it could be obtained quite free from admixture with the central portion. Schäfer and Herring (151) found this to be the case also with the substance which acts as a diuretic. Improbable as it would appear at first sight, the conclusion seems inevitable that it is the nervous portion proper which contains the substance or substances having much pronounced pharmacodynamical properties different from those possessed by other nervous tissues.

Bell (10) has recently revived the suggestion that it is probably the epithelial cells of the posterior lobe and those of the pars intermedia that are responsible for the pressor base [see, however, Swale Vincent (175)]. So far as I am aware, no further experiments upon this point have been performed, but Schäfer (150) has changed his opinion, and believes that it is the function of the pars intermedia to

produce a "colloid" material which contains active principles or hormones acting upon the heart, bloodvessels, and kidneys.

Emile-Veil and Boyé (45) have recently found that an extract of anterior lobe retards coagulation of the blood, while extract of the posterior lobe accelerates it. On 7 hirudinized blood the extract of the lobes of the rabbit's pituitary does not produce much effect, but on the blood of hæmophilics the extract of the posterior lobe corrects the incoagulability, while extract of the anterior lobe augments it. On this subject see also Livon (96).

Sandri (149) has recently come to the conclusion that the active principle is furnished by the posterior portion of the epithelial lobe, which portion always remains adherent to the nervous lobe.

#### **E. Extirpation Experiments upon the Pituitary Body.**

The first to perform experimental extirpation of the pituitary was Horsley (84) in 1886. Since that date a large amount of experimental work in this direction has been carried out. The earlier investigations yielded contradictory results. In some cases death occurred soon after the operation, while in others the animal lived for a long time. Among these earlier workers may be mentioned Friedmann and Maas (58), Lo Monaco and Van Rynberg (101), Marinesco (108, 109), Vassale and Sacchi (174), Narbutt (120), Aschner (4), and Gemelli (61, and more recent papers). Paulesco (126, 127) was one of the first to definitely urge that the organ is essential to life. This view has been controverted by Gemelli (60), but Paulesco's view has gained strong support from the careful work of Reford and Cushing (139) and Cushing (34).

The methods adopted before Paulesco's work were not satisfactory, as the attempts were made either through the base of the skull or through the vertex. It is probable that in many instances the operation was not complete, and that in others there was loss of life from hæmorrhage and injury to the brain. The method adopted by Cushing is a modification of that of Paulesco—namely, a lateral and intracranial approach under the temporal lobe, by resecting the arch of the zygoma.

Cushing's experiments were performed upon dogs, and he reports that the pituitary body is essential to the maintenance of life, though the important fact has been brought out by Dr. Crowe (one of Cushing's collaborators) that young dogs survive the total loss of the gland for a considerably longer period than do older dogs: and it was possible to prolong life for a time, though not indefinitely, by immediate or antecedent transplantation of the anterior lobe, or by post-operative injection of its extract [see also Crowe, Cushing, and Homans (32)].

After total extirpation of the pituitary body the animals usually recovered quite well from the effects of the operation. Though less active and responsive than after other operations, nevertheless, on the day after the hypophysectomy, the animals were normal. After some hours, however, they became lethargic and indifferent. From this condition they passed into a comatose state, with a striking incurvation of the spine, a slow respiration with a long-drawn inspiratory act, a feeble pulse, a perfectly limp musculature, and often a subnormal temperature. The transition from coma to death was almost imperceptible. It seems, then, from these experiments of Cushing, that total removal of the gland leads, in the course of days, or at most of a few weeks, to death, with a peculiar and characteristic train of symptoms (apituitarism or cachexia hypophyseopriva).

No effects (except some sexual disturbances) follow the removal of the entire posterior lobe (pars nervosa and its epithelial investment), though some of the epithelium of the pars intermedia usually remains attached to the tip of the infundibulum after the operation. On the other hand, partial removal of the anterior lobe leads in some cases to adiposity, sometimes associated with polyuria, glycosuria, shedding of hair, lessening of sexual activities, and atrophy of testes and ovaries.

It cannot be admitted that these experiments are conclusive as to which parts of the pituitary is essential to life. As remarked by Schäfer (150), it is almost impossible to remove one part alone, so closely are they dovetailed into one another; indeed, the pars nervosa and the pars intermedia are in direct continuity, and both are almost com-



pletely enclosed within the pars anterior. It has been stated that the mere separation of the pars nervosa from the infundibulum has sometimes proved equally fatal with the actual removal of the gland [Paulesco (126, 127)].

More recently Cushing (33, 35) has given a further account of his work. His conclusions are that removal of the posterior lobe gives rise to no symptoms, while extirpation of the anterior lobe alone gives rise to all the serious ill-effects of a total pituitary extirpation. In from thirty-six hours to two weeks after the operation, according to the age of the animal, the symptoms of "cachexia hypophyseopriva" supervene. In the interval the animal is normal, except, perhaps, some temporary glycosuria, with or without polyuria. The onset of the cachexia is made manifest by inactivity, uncertain movements, lowering of the body temperature, tetany-like contractions of muscles, and, finally, coma and death. Histological changes were found in the thyroid and in the testis. Partial removal of the anterior lobe in young dogs leads to a prolongation of the period of infancy, while in several adult animals there has been a reversion to the infantile type. The animals grow fat, and the external organs of generation become atrophied. There is a disappearance of the spermatozoa from the testes, and there are changes in several other glands. The glycosuria and the growth of adipose tissue which may be observed in young animals are probably due to these secondary changes.

Cushing thinks that acromegaly and gigantism are due to a hypersecretion of the anterior lobe of the pituitary.

Dr. Handelsmann and Sir Victor Horsley have quite recently published a preliminary note based on a renewed experimental investigation on the pituitary body (74). They have made experiments on 54 animals—namely, 20 cats, 21 dogs, and 13 monkeys—in which the pituitary gland was reached by either of two methods—(1) temporal, (2) palatal. The second method they employed only in the cat.

In 15 animals (2 cats, 9 dogs, and 4 monkeys) complete extirpation of the pituitary body was performed. Eight animals died within forty-eight hours from shock, hæmorrhage, or infection. Of the remainder, three died within four days without symptoms of the cachexia described by Cushing.

There remain four cases (all monkeys). In three of these death occurred naturally on the thirteenth, fourteenth, and thirty-ninth days, and one animal was killed in good health on the one hundred and fifteenth day. In the three animals which died naturally there were no characteristic symptoms such as those described by Cushing. Further, the authors observed a parallel death-rate in animals in whom incomplete extirpation had been made.

It is clear that the results in this series of experiments are quite different from those obtained by Paulesco and Cushing.

Staderini (163) believes that extirpation experiments have given contradictory results in the hands of different observers, because operators have not always taken count of the "lobi laterales" and the "lobulus præmamillaris" described by him in the cat and in the ox (161, 162). Perna (131) has given a full description, with illustrations, of a "posterior glandular prolongation" in the human subject. The nomenclature of these different "accessory pituitaries" seems to be considerably confused, and the whole subject is in need of a systematic description.

It will be readily concluded that it is yet too early to draw any positive conclusions from the result of extirpation experiments upon the pituitary body.

#### **F. The Comparative Physiology of the Pituitary Body.**

Professor Osborne, working in conjunction with the present writer (123), showed that extracts of the pituitary body of the cod produce effects upon the heart and blood-vessels similar to those of extracts of the mammalian posterior lobe.

Schäfer and Herring (151) demonstrated that extracts made from the cod's pituitary produce kidney dilatation and diuresis when injected, just as do extracts from the mammalian posterior lobe.

The subject has been recently more thoroughly investigated by Herring (77). This observer finds that the posterior lobe of the pituitary body of the fowl produces an effect on blood-pressure, kidney volume, and urine secretion, which is very similar to that produced by extracts of the posterior

lobe of the mammalian pituitary. It was found to be impossible to determine whether the active principles in the posterior lobe of the bird's pituitary are products of the epithelial cells of the *pars intermedia*, or are formed solely in the nervous substance. No distinct effects were produced by extracts of the avian anterior lobe.

In regard to Teleostean fishes, extracts of the anterior lobe proper—chromophil portion of Sterzi and Gentes—have little physiological effect. The general effect of extracts of the posterior lobe is similar to that brought about by extracts of the mammalian and avian posterior lobes. In Teleosts the cells of the *pars intermedia* predominate in the posterior lobe, and are inseparable from the *pars nervosa*, so that one cannot determine which produces the active material. According to Herring, both are probably concerned, for wherever cells of *pars intermedia*—chromophobe cells of Sterzi—are bound up with *pars nervosa*, extracts of the resulting tissue produce the effects on blood-pressure, kidney volume, and urine secretion which have been associated with extracts of the posterior lobe of the mammalian pituitary. Extracts of the *saccus vasculosus* are practically inactive, and Herring supports the supposition of Gentes that this structure has a function similar to that of a choroid plexus.

The Elasmobranch pituitary, as we have already seen, is quite different in structure from the pituitary bodies of mammals, birds, and Teleosts. There is no differentiation into anterior and posterior lobes. According to Herring, there are no cells precisely corresponding to those of either the anterior portion or the *pars intermedia* of the mammalian body. The presence of the true nervous portion seems also doubtful. Extracts of the Elasmobranch pituitary give rise to no characteristic physiological effects.

### G. Disease of the Pituitary Body—Acromegaly.

#### 1. *Introductory and Historical.*

Acromegaly, a disease characterized by enlargement of certain bones of the body, especially of the hands and feet, was first described by Marie, of Paris, in 1886 (106, 107).

It was observed by Marie that the disease is associated with tumours of the pituitary body. It had, however, been previously described under other names, as "hyperostosis of the entire skeleton" by Friedreich, as "general hypertrophy," or "makrosomie" by Lombroso, as "giant growth" by Fritsche and Klebs [Tyson (173)]. A full account up to date is given by Arnold (3).

### 2. *Symptoms.*

The affection begins in the adult, sometimes during adolescence. It is characterized by a progressive increase of volume of the face, of the hands, and of the feet. The face soon presents, as a result of these changes, a strikingly characteristic appearance of deformity—an enormous nose, a lower lip voluminous and pendulous, and a protruding chin. In addition to the overgrowth of bone, there is also hypertrophy of the connective tissues. In the later stages the spinal column may be involved, and there is dorsal kyphoscoliosis.

The muscles may be atrophied, and the skin is not thickened.

Headache and affections of the eyesight are common symptoms, and polyuria has been often recorded. Mental dulness and a sense of fatigue are also mentioned. There may be some disturbances of the reproductive system.

### 3. *Ætiology and Onset.*

Acromegaly has been sometimes ascribed to syphilis, or some other specific infection. Heredity has also been claimed as having some part in the causation. There is, however, no sufficient evidence that any of these bear any essential relation to the disease.

The disease occurs, perhaps, most frequently in early adult life, between the age of puberty and the thirtieth year. It is more common in women than in men. The onset is gradual.

### 4. *Metabolism in Acromegaly.*

If acromegaly be, in fact, due to a hypersecretion of the pituitary body, we should naturally expect that in this disease the metabolism would be modified in the same

direction as in animals fed upon pituitary substance. The few experiments which have been performed upon acromegalic patients have given contrary results [Salomon, quoted by Richter (142)].

#### 5. *Morbid Anatomy.*

The bones appear to undergo a true hypertrophy in the majority of cases, though it is stated that the superior maxillary appears to be larger on account of a simple dilatation of the antrum. In the long bones the enlargement affects the ends as well as the shaft.

The view which has the greatest number of adherents at the present time is that the characteristic lesion in acromegaly is adenoma of the pituitary. This belief was first definitely put forward by Benda (12, 13, 14, 15, 16). Previously the tumour had been known by various names, perhaps most frequently as a "round-celled sarcoma." Hanau [quoted by Fischer (52)] had previously suggested that the typical growth is an adenoma; and Löwenstein (99, 100) has given a lucid account of the development of this adenomatous tumour.

Other tumours of the pituitary do not appear to give rise to acromegaly. Thus, Pende (128, 129) notwithstanding (see p. 371), Erdheim (46) states that tumours of the "pharyngeal pituitary" (remains of the pituitary duct) never give rise to acromegaly. Several authors report cases of pituitary sarcoma without any signs of acromegaly [Cagnetto (23, 24), Kollarits, quoted by Fischer (52)]. The same applies to carcinoma [Formanek (54)] and endothelioma [Addari (1)].

Microscopical examination shows that the tumour in acromegaly has all the characters of the anterior lobe of the pituitary body. The various kinds of cells found in the latter structure are also regularly found in the tumour.

Thus, it would appear that an adenoma of the anterior lobe of the pituitary is the essential lesion characteristic of acromegaly.

#### 6. *Pathogeny.*

Various theories have been sustained as to the origin and essential cause of the symptoms of typical acromegaly. It

was suggested by Freund (57) that acromegaly is simply an anomaly of development. Some writers have imagined that the essential lesions in acromegaly are in the thyroid or in the thymus. It has also been suggested that defects in the reproductive organs may be responsible for the conditions (*vide infra*, p. 390). The nervous system has from time to time been called in question. But of late years most of the theories advanced have assumed that the pituitary is in some way affected in all undoubted cases of acromegaly.

Of the pituitary theories, the first was that of the original describer of the disease—Marie. His view was that acromegaly is due to destruction of the pituitary, and therefore to complete abolition of its function. Those who still uphold this view look upon the gland as supplying a hormone which regulates the growth of the skeleton, which growth, in the absence of such regulation, proceeds abnormally. Bleibtreu (19) has recently published a record of a case of acromegaly, in which he states that there was total destruction of the pituitary gland.

The opposite view, that the symptoms of acromegaly are due to a hypertrophic condition of the pituitary, more particularly of its anterior lobe, is held by Tamburini (170) and Woods-Hutchinson (179, 180, 181), and has recently been advocated by Schäfer (150) and by Fischer (52). The most important argument in favour of this view is the frequency with which a true adenoma has been reported as occurring in typical cases of acromegaly. It may be supposed that, according to this theory, the anterior lobe of the pituitary body furnishes an abnormal, an excessive, quantity of some hormone which stimulates bone growth, and that, in consequence, the growth of bone itself becomes excessive.

The cases referred to above in which after death the substance of the pituitary has been completely destroyed and replaced by a malignant growth, would seem to present a certain difficulty in the way of acceptance of the hypersecretion theory. They would seem, in fact, to furnish important evidence that the symptoms of acromegaly have been brought about as the result of the suppression of an internal secretion. But, as Professor Schäfer suggests, it

is possible to assume that the tumour at its beginning was non-malignant, and that the malignant character has become developed shortly before death, and that death has resulted from entire suppression of the function of the gland, owing to destruction of the normal glandular cells by those of a malignant nature ; for it appears possible that complete destruction of the gland is incompatible with continuance of life.

Since, after destructive disease of the reproductive organs, the pituitary is found to be enlarged, it has been suggested [Mayer (112)] that the actual commencement of the mischief in acromegaly may be in the ovary or the testis.

The pathogeny of acromegaly thus appears to be analogous to that of exophthalmic goitre, the first being due to a hyperfunction of the pituitary, the second to a hyperfunction of the thyroid gland.

#### 7. *Course and Event of the Disease—Diagnosis, Prognosis, and Treatment.*

The disease runs a slow and prolonged course, and goes on to a fatal issue.

The diagnosis is usually a matter of no great difficulty. From *osteitis deformans* and from *arthritis deformans* it may be distinguished because the enlargement is general, instead of affecting only the shaft, as in osteitis deformans, or the ends, as in arthritis deformans. In osteitis deformans, too, as pointed out by Marie, the face is triangular, with the base *upward*, while in acromegaly it is ovoid, with the large end downward. In congenital progressive hypertrophy, or "giant growth," only one limb becomes affected, and the shaft of the bone is involved [Tyson (173)].

But the differential diagnosis from certain diseases of the nervous system, and in particular from *syringomyelia*, is sometimes very difficult, or even impossible.

In affections of the spinal cord enlargements of the extremities are liable to occur, and especially is this true in *syringomyelia*. Fischer (52) gives several examples from Schlesinger (155), Holschewnikoff (83), and M. B. Schmidt (156). It is stated that *syringomyelia* may give rise to the typical clinical and anatomical features of acromegaly. If this is true, then it will be absolutely im-

possible in certain cases to make a correct diagnosis during life, and it must have frequently happened that cases of syringomyelia have been described as "acromegaly without tumour of the pituitary." The suggestion has been tentatively put forward that the hypersecretion of the pituitary may, after all, produce the condition of acromegaly by action upon the nervous system [Fischer (52)].

The prognosis is bad, and all treatment hitherto attempted seems to be without avail. Naturally, treatment with pituitary preparations has been tried. This, of course, has been done on the hypothesis that acromegaly is due to diminished action on the part of the gland. The results are unsatisfactory, and even definitely unfavourable results were sometimes obtained [Sternberg (165)]. No reduction can be effected in the size of the extremities by internal administration of the gland [Marinesco (110), v. Cyon (37)]. Magnus-Levy (104) records a case of acromegaly treated with pituitary substance. Symptoms arose which recalled features of Graves's disease—marked perspiration, polyuria, and alimentary glycosuria [Batty-Shaw (159)].

It seems, from all that has gone before, that the only rational treatment for acromegaly is a partial extirpation of the pituitary body. This has been definitely suggested by Sir Victor Horsley.<sup>1</sup>

It is possible that Masay's (111) pituitary antiserum might be of some service.<sup>2</sup>

#### 8. *Other Conditions involving Pituitary Hyperfunction.*

There are reasons for thinking that many forms of gigantism are due to hyperfunction of the pituitary, and probably to hyperfunction of the anterior lobe. In these cases there is rarely, if ever, a definite adenoma of the gland. But it is possible that the structure might manufacture certain substances in excess of the normal, without overgrowth of the gland as a whole, but simply by multiplication of certain cells.

<sup>1</sup> Recent papers on the surgery of the pituitary are : Hirsch (80), Ranzi (135), Fein (51).

<sup>2</sup> A recent account of acromegaly is given by Cantani (25).



### 9. Conditions involving Hyposecretion of the Pituitary.

Frölich (59) was the first to point out that in cases of pituitary tumour without acromegaly there may be manifested a peculiar syndroma, characterized by the accumulation of fat and disturbance of the genital functions—*degeneratio adiposo-genitalis*. Erdheim [quoted by Fischer (52)], however, is of the opinion that not only pituitary tumours, but other growths in this region of the base of the brain, may give rise to a similar train of symptoms. It is thought by Fischer that the effects are due to damage to, or destruction of, the posterior lobe of the pituitary body.<sup>1</sup> The experiments of Cushing (32, 33, 34, 35), however, would seem to teach that it is deficiency of function of the anterior lobe which leads to *degeneratio adiposo-genitalis*.

So far, the only symptom of acromegaly which appears to bear a direct relation to the functions of the pituitary, as revealed by physiological experiment, is polyuria. But recently some experimental work has been performed, in order to ascertain what is the relation between the activity of the gland and overgrowth of skeletal tissues. Some account of this work will now be given.<sup>2</sup>

### H. Feeding and Metabolism Experiments.

The first metabolism experiments were performed by Schiff (85), who administered pituitary substance (Merck's tablets) to a healthy man, to a man suffering from paralysis agitans, and to a case of acromegaly. He found that there was no influence on the nitrogen in any case, but that the phosphorus output in the two diseased cases was increased. The increase took place in the fæces, and Schiff attributed it

<sup>1</sup> Insufficiency of the secretion of the posterior lobe is stated to increase the tolerance of the animal towards sugar (Goetsch, Cushing, and Jacobson, 63).

<sup>2</sup> The following are references to some recent papers on the pathology of the pituitary body: Erdheim (47), Hagenbach (71), Konjetzny (92), Hayashi (75), Aschner (5). Wurmbrand (182), from the histological study of three operated cases of acromegaly with pituitary tumour, concludes that in malignant adenomata of the pituitary body one may get either typical acromegaly or Frölich's syndroma ("*degeneratio adiposo-genitalis*," see above), or a combination of the two. In one of the three cases there was a persistent thymus and status lymphaticus.

to katabolism of bony tissue. Neither calcium nor magnesium was estimated, and, as pointed out by Malcolm (105), the conclusion arrived at assumes that bone was the only phosphorus-rich tissue which was affected, whereas it is possible that the increase may have been due to nuclein.

Moraczewski (118) studied the metabolism of a case of acromegaly, and found that on simple diet alone there was a marked retention of nitrogen, phosphorus, calcium, magnesium, and chlorine. This he puts down to the increased growth of the tissues, soft as well as bony. On giving pituitary, the nitrogen output was increased, also that of phosphorus, while the calcium was unaffected, or even slightly retained.

Oswald (124) experimented on a dog with some pituitary-gland preparations, and found no effect on the nitrogen or phosphorus in the urine.

Malcolm (105) found that the anterior lobe of the pituitary, when administered in the dry form, tends to cause a retention of nitrogen; the dried nervous portion has a similar effect. The fresh entire gland in large doses has an opposite effect, and increases the output of nitrogen.

The anterior lobe caused a retention of phosphorus, while the posterior caused a loss, followed by a retention.

Both the dried glandular and nervous portions gave an increased output of calcium (on a calcium-rich diet), but while the excretion of calcium in the former case was accompanied by an increased output of magnesium—in the fæces, at any rate—the latter was not, or not to the same extent, so accompanied. This points to the “nervous” portion having had a katabolizing influence on bony tissue. Fresh gland substance gave no increased calcium output (diet poor in calcium), but rather a tendency in the opposite direction. The magnesium output was at first increased—to a greater extent than can be accounted for—by the increased katabolism of protein tissue which took place simultaneously (if one may so interpret the increased nitrogen output). In the post-pituitary period the balance swings in the opposite direction. This corresponds to the effect of the (dried) glandular portion, which forms five-sixths of the entire gland.

In the case of nitrogen and calcium, the fresh gland has an opposite effect to that of the dried, pointing to the probable existence of more than one active substance. According to Malcolm, the nervous portion is probably the more active, as shown by the duration of the effect—*e.g.*, increased amount of faeces and increased calcium output—lasting over the succeeding normal period, while with the glandular portion effects usually cease with cessation of administration.

Cerletti (26, 27, 28) injected pituitary emulsion intraperitoneally into young animals, and found that the bones of the animals receiving the emulsion were, after some time, as compared with controls, somewhat shorter as regards the diaphyses, but larger as regards the epiphyses. This appears to indicate a retardation in growth of the bones.

Sandri (148) fed young mice and guinea-pigs with pituitary emulsion, and states that this caused an arrest of growth.

Professor Schäfer (150) has recently planned and in part carried out a series of feeding experiments on white rats, both young and adult. In a preliminary series he finds that feeding with the anterior lobe causes some increased rate of growth. This result differs from that of the Italian authors above referred to, but Schäfer does not wish to draw positive conclusions until further experiments have been performed.

Exhibition by the mouth of an active water extract of the posterior lobe may greatly increase the amount of urine secreted. This does not always occur—as, indeed, is the case, also, with intravenous injection—and the activity of the gland in promoting diuresis often appears greatest in cases in which the amount of urine which was previously being passed is less than usual.

Schäfer also records a distinct increase in the secretion of urine in two children, to whom an active extract of the posterior lobe of the ox pituitary had been administered. He further recalls similar observations by Marinesco (109) and Azam (6) in cases of acromegaly and infectious fevers respectively.

Franchini (55) has performed a series of experiments in

which extracts from the pituitaries of oxen and horses were administered to rabbits and guinea-pigs. It is reported that the metabolism, especially the inorganic metabolism, undergoes serious changes. The calcium and magnesium metabolism is much reduced, and the same applies to the phosphorus metabolism, only to a less extent. In the circulating blood there is an increase in the calcium and magnesium. In rabbits there is occasionally glycosuria.

Besides this toxic action on rabbits and guinea-pigs, the extracts have a special injurious influence upon the alimentary canal, giving rise to ulcerations and hæmorrhages, which probably depend in part on alterations in the trophic nerves. The greatest toxicity is shown when the substance is injected into a vein, but very considerable effects are also produced when the material is administered by subcutaneous injection, or when it is taken into the stomach. Digestion *in vitro* reduces to some extent this toxic action.

These effects are produced by injection of the posterior lobe substance, to some extent by the epithelial reflection upon this lobe, but not at all by extracts of the anterior lobe (see discussion on p. 381).

The transplantation of additional pituitaries into an animal causes increase in weight, owing to an increase in the amount of pituitary secretion. The increase is partly due to increased stature, but partly, also, to the accumulation of fat [Exner (49, 50)].

According to Mochi (115, 116, 117), pituitary extracts cause an increase of metabolism and shortening of the duration of life in starving rabbits. As the inanition progresses, there is a very considerable increase in the nitrogenous elimination, but also simultaneously an important increase in the phosphorus metabolism.

The elimination of phosphorus and calcium far surpasses that of the nitrogen. If one determines the amount of excreted phosphorus of muscular origin (calculated from the quantity of nitrogen estimated), and subtracts this amount from the total quantity of phosphorus excreted, one obtains numbers which stand in the same proportion to those of total excreted calcium, as these two elements do to each other in bone.

### I. Grafting Experiments.

It has already been noted that Cushing found that it is possible to prolong life for a time, though not indefinitely, by immediate or antecedent transplantation of the anterior lobe.

Schäfer (150) has recently reported a series of grafting experiments which were instituted in order to investigate the effects of pituitary secretion upon growth. But no permanent graft was obtained, and the experiments have so far thrown no light on the question. The only distinct effect noticed was with the posterior lobe, which caused a temporary increase in the flow of urine. As the implanted gland soon became absorbed, this result is probably to be looked upon simply as the effect of the administration of an equivalent amount of pituitary extract. It is possible, however, that the transplanted glands may have functioned for a brief period.

### J. Stimulation of the Pituitary Body "in situ."

As we have seen in a previous section, Cyon (37) has employed the method of direct excitation of the gland. He exposed the hypophysis by trephining the base of the skull beneath the sella turcica. Then he exerted light pressure upon the gland by means of a small pad of cotton. He observed immediately a considerable variation in the blood-pressure and in the number and intensity of the heart-beats. These variations occurred to some extent as the result of the trephining, but were much exaggerated by a very slight electrical stimulation. Cyon worked with rabbits, and noted a considerable slowing of the heart-beats, with increase of amplitude.

Pirone (134) was able to obtain slowing of the pulse and acceleration of the respiration. But he obtained the same effect by electrically stimulating different points of the inferior aspect of the brain, even after preliminary ablation of the pituitary. Masay (111) has been unable to verify the statement of Pirone. Cyon states, also, that, after ablation of the hypophysis, compression of the abdominal

aorta causes no change in the carotid pressure. He concludes from this experiment that the hypophysis is the point of departure of reflexes which regulate the blood-pressure.

Masay (111) has repeated these experiments, and obtains results similar to those of Cyon. The effect of direct stimulation of the gland he attributes, as do Schäfer and Herring, to an increased discharge of the internal secretion into the blood-stream, where it produces the usual result of the extract upon the heart and blood-pressure. The effect of ablation of the pituitary in abolishing the rise of carotid pressure on compressing the aorta is not easy to explain, though Masay is inclined to attribute it to operative shock.

Schäfer (150) reports that in dogs partial injury to the pituitary by means of a thermo-cautery or mechanical agents induces marked diuresis. This result is specially interesting in relation to the polyuria which occurs in injuries and tumours affecting the base of the brain. Such polyuria is more likely to occur when the hypertrophy involves the pars intermedia, or when this part is stimulated mechanically by the adjacent growth [see, also, Rosenhaupt (145), Sternberg (164), and Borchardt (20)].

#### **K. The Question of a Functional Relationship between Thyroid and Pituitary.**

Changes in the pituitary after extirpations of the thyroid and parathyroids have already been referred to (p. 346; see Fig. 84, p. 347). The views of Cyon and others as to a functional relationship between thyroid and pituitary have also been mentioned. It only remains to make reference in this place to some experiments of Masay (111) in opotherapy, with the object of ascertaining whether extract of pituitary can replace the internal secretion of the thyroid, and prevent ill-effects after removal of the latter organ.

Masay performed thyroidectomy in dogs of different ages. As soon as symptoms came on he injected subcutaneously an emulsion prepared from dry pituitary extract. The results were entirely negative, so that these

experiments, so far as they go, do not lend support to the view that the pituitary secretion can replace that of the thyroid.

#### L. Pituitary Insufficiency and a Pituitary Antiserum or Cytotoxin.

Some account of pituitary insufficiency has already been given under the heading "Extirpation of the Pituitary Body." There is no doubt, however, that, after ablation of the pituitary, even by the best methods and the most elaborate surgical precautions, it is not always possible to distinguish symptoms due to absence of the pituitary secretion from those due to traumatism.

Accordingly, Masay (111) has attempted to produce pituitary insufficiency by another method—namely, that employed by Demoor and v. Lint (22), in order to obtain an "antithyroid serum."<sup>1</sup>

Guinea-pigs were injected intraperitoneally with an emulsion of dog's pituitary at intervals of two days. After three, four, or five injections the blood of the guinea-pig was collected and centrifugalized, and the serum (about 10 c.c.) was injected under the skin of a dog. Masay gives his results in considerable detail, and the effects upon the animals are shown by a series of illustrations. After a certain number (usually two or three) of such injections the dogs show symptoms such as loss of flesh, muscular weakness, especially in the hind-limbs, changes in the skeleton and in the structure of the pituitary—the symptoms constituting, according to Masay, a veritable *cachexia hypophysipriva*.

As pointed out by Schäfer, such experiments require to be multiplied and carefully controlled before the results can be accepted as produced by changes in the pituitary body [see also Parisot (64)].

<sup>1</sup> Cytotoxins have been described for almost all the organs of the body. The two best known are hæmotoxin [Jules Bordet (21)] and spermotoxin. The latter is stated to arrest the movements of spermatozoa, and its action is very easily controllable.

### M. Chemistry of the Pituitary Body.

There is at the present time nothing definite known as to the chemical nature of the active principle or principles of the pituitary body.

Schäfer and Vincent (152), who described a pressor and a depressor substance, found that the latter could be separated from the former on account of the fact that it is soluble in alcohol, in ether, and in normal saline solution. It is now recognized that this depressor substance is common to all animal tissues (see p. 27).

Whether we have to deal with separate pressor and diuretic substances is not yet determined. Schäfer and Herring (151) contend that two active principles exist in pituitary extracts, one acting on the circulatory system, the other specifically on the kidney. Dale (40) does not consider the evidence on this point to be satisfactory, and gives some experimental results which seem to point in the opposite direction. Schäfer and Herring state that peptic digestion reduces the action of the extract on the blood-pressure without affecting the action on the kidney, but that neither action is affected by tryptic digestion. They also obtained results which they regarded as indicating that oxidation by  $H_2O_2$  destroys the pressor action more quickly than the diuretic action. Dale has failed to confirm these results.

According to Dale, the action of extracts of the posterior lobe of the pituitary body is a direct stimulation of involuntary muscle, without any relation to innervation. This indicates an important difference between such action and that of adrenalin. The action is most nearly allied to that of the digitalis series, but the effect on the heart is in this case slight, that on plain muscle intense.

Dale further reports that no true immune reaction is produced by repeated injection of the extract. The active principle is excreted in the urine.



**N. Some General Questions as to the Internal Secretion of the Pituitary Body—the Relationship between the Pituitary and the Reproductive Organs.**

Within the last few years there has been a steady accumulation of facts pointing to important physiological relationships between several of the glands having an internal secretion. In earlier years many suggestions were offered from time to time that the "ductless glands" all worked together for the common needs of the economy; but these suggestions were for the most part based upon *a priori* considerations, and arose from the fact that thyroids, adrenals, and pituitaries were grouped together in a chapter of physiology wherein it had to be recorded that our ignorance of these structures was complete.

But the modern growing belief in the functional inter-relationship between the various glands with an internal secretion is based upon sound experimental evidence, and careful observation in the realms of anatomy, physiology, pathology and clinical medicine, surgery, and gynæcology. The conception of relationship applies not only to the structures commonly referred to as the ductless glands, but also to some other structures having an internal secretion—viz., the pancreas and the reproductive organs.

In clinical medicine lesions or functional disturbances in several of the organs mentioned give rise to a clinical picture which is sometimes referred to as the "pluri-glandular type." In such cases it is sometimes difficult to decide as to where was the primary lesion.

Many instances of functional relations between the different glands have been given in the preceding pages. To recapitulate these would involve unnecessary repetition. Pineles (132, 133) has pointed out some interesting relationships between acromegaly and myxœdema and some other diseases of internally secreting glands, such as diabetes (132, 133). The work of Eppinger, Falta, and Rudinger (p. 216) points to a physiological relationship between adrenal, thyroid, and pancreas. We have also discussed the connection between thyroids and parathyroids and between both these organs and the pituitary. Tandler [cited by Kohn (90)] states that in cases where castration

has been performed early in life there is enlargement of the pituitary body. It has even been suggested that the abnormalities of growth in castrated animals may be due to changes in the pituitary.

According to Kohn (90), there is nothing to suggest that the posterior lobe has an internal secretion, in spite of all the results of experiments involving the injection of extracts. There is a considerable difficulty about this problem. We have seen (p. 381) that the extracts having powerful effect upon the blood-pressure and the flow of urine are obtained from the posterior lobe, and not from the epithelial layer which covers it. This view seems to be borne out by the experiments of Franchini (see p. 395). Now, the posterior lobe proper (excluding the epithelial layer) consists of neuroglia, pigment, and occasional nerve cells. It is extremely difficult to imagine how such a structure can be regarded as a secreting gland. We have already had to discuss an analogous problem in regard to the chromophil cells (see p. 213 *et seq.*). In the case of these latter, however, there is a certain amount of histological evidence in addition to the experimental, which leads us to the conclusion that they manufacture an internal secretion. According to Kohn, there is no such thing as a true infundibular gland in mammals, although such a structure is found in lower vertebrates.

There can, however, be no dispute about the glandular nature of the anterior lobe. It has, as we have already seen (p. 368), all the characters of an "epithelial body," of an internally secreting gland, with several varieties of characteristically staining cellular elements.

As Kohn (90) points out, we know, after all, very little about the normal functions of the pituitary—no more, in fact, than we know about those of any other of the ductless glands. But we do know many of the striking results of disturbances of, or departure from, the normal functions. And the extraordinary degree of the resulting abnormality not only gives us a measure of the importance of the normal functions, but may also throw out hints as to the nature of such functions.

What happens, then, in cases of disturbances, absence, excess, or defects of the pituitary secretion? So far as is

possible this question has been answered in the preceding pages dealing with experiments upon and diseases of the pituitary body. It is only necessary to add that there is some evidence that the young animal depends for its chemical stimuli to growth not only upon the adrenal and thyroid bodies, but also upon the pituitary.

As bearing upon the relationship between the pituitary and the sexual functions, the work of Erdheim and Stumme (48) is of great interest. These authors describe three types of cell in the glandular part of the pituitary :

1. Eosinophile granular cells (chromophile 1 ; acidophile).
2. Basophile granular cells (chromophile 2 ; basophile).
3. " Hauptzellen " (chief cells ; chromophobe cells) (see p. 369).

The chief cells have very badly defined and poorly staining protoplasm. In pregnancy the pituitary may become hypertrophied to two or three times its normal size. The increase consists entirely in the glandular portion. There are no longer to be seen either chromophile or chromophobe cells, but there are peculiar large, finely granular cells (the " pregnancy cells "). These are derived from the chief cells, which grow from the centre of the alveolus, and occupy a large part of the secretory structure. These slowly retreat again during the period of involution.

The pituitary during pregnancy resembles an epithelial tumour. The increase in the amount of secretion is seen by the fact that one can squeeze a milky juice out of the gland. The hypertrophy persists to a certain degree, even after pregnancy, so that the weight of the gland in a multipara may be three times as great as that of a normal gland.

Erdheim and Stumme (48) thought that the hypersecretion of the pituitary in pregnancy is manifested by an enlargement of the hands and lips which is sometimes observed. Occasionally, also, there may be more striking symptoms, due to the effects of the pituitary tumour. Among these may be mentioned hemianopia.

Mayer (112) is of opinion that the pituitary changes are

due to functional changes in the ovary—in other words, that the pituitary may function vicariously for the ovary. A relation between pituitary and ovary is shown by the fact, already mentioned, that in castrated women and animals there is frequently enlargement of the pituitary. Further, after destructive diseases of the reproductive glands the pituitary reacts by hypertrophying. Mayer is even inclined to believe that the actual commencement of the mischief in acromegaly may be situated in the reproductive organs.

#### O. The Use of Pituitary Extracts in Medicine, Surgery, and Gynæcology.

Reference has already been made to the use of pituitary extracts in acromegaly. We have seen that they have not been found to be beneficial in this disease. Nor should we expect them to be of service if acromegaly be, in fact, due to a hypersecretion of the gland.

But there are many other conditions in which pituitary preparations have been recommended and employed.

In conditions of *shock*, pituitary preparations are believed to be of more value than adrenin. This is due partly to the fact that pituitary preparations ("pituitrin," "infundibulin," etc.) keep the blood-pressure raised for some considerable time, while the effect of adrenin is very fleeting. Saline infusions should, however, be used; reliance should not be placed on the pituitary extract alone.

Owing to its powerful action on the uterus (see p. 379), pituitary substance is now employed in many *obstetric conditions* [Bell (10)]. The action on the uterus was first noticed by Dale (38), and has since been studied by several observers. Foges and Hofstätter (53) have obtained results similar to those of Dale and Bell, and recommend pituitrin in post-partum hæmorrhage. Other observers now recommend the use of the drug in labour [Hofbauer (82), Gottfried (65)].

Bell (10) strongly recommends "infundibulin" in cases of *sluggish intestinal peristalsis* and paralytic distension of the intestines.

It is probable, also, that the diuretic effect of pituitary extracts [discovered by Magnus and Schäfer (48) ; see also Schäfer and Herring (151)] may be of clinical value.<sup>1</sup>

<sup>1</sup> Since the above has been in the press two important papers on the pituitary body have appeared. These must be briefly referred to here.

Benedict and Homans (*Journ. of Med. Research*, February, 1912) report that extirpation of the pituitary body retards the growth of young animals, and hinders the development of sexual activity. There is an excessive deposition of body-fat as well as thickening of the skin and falling out of the hair. The change in appearance of older animals surviving nearly complete removal is hardly noticeable.

Houssay (*Riv. de la Soc. Med.*, Argentina, 1911) agrees with Osborne and Vincent that it is the *purely nervous* part of the pituitary body which furnishes the active extracts. The same author claims to have isolated the crystalline active substance of the posterior lobe.

## CHAPTER XVI

### THE FUNCTION OF THE PINEAL BODY

MUCH attention has been devoted to the pineal body from the standpoint of comparative anatomy. Its relationship to the pineal eye of lower vertebrates seems to have led to the conclusion, which may, after all, turn out to be premature, that the pineal body of mammals is a purely vestigial organ, and no longer of any functional importance. Notwithstanding the numerous investigations which have been carried out upon the comparative anatomy and development of the organ, there appear to be few careful and detailed descriptions of the microscopical structure in Mammalia. Moreover, the number of essays in the direction of a physiological study of the structure are very limited. The general appearance of the body on microscopical examination certainly suggests the possibility of a secretory function, and, as we shall see, there is some evidence that the pineal body controls in some way or other (possibly by means of an internal secretion) the early growth of the individual.

#### **Anatomy and Development of the Pineal Body.**

The pineal body, or pineal gland (conarium),<sup>1</sup> is a small pinkish body situated underneath the posterior region of the corpus callosum, and resting upon the anterior elevation of the corpora quadrigemina.

A section through the diencephalon of an early human embryo shows the "roof-plate" and the "floor-plate." At the posterior end of the former is an elevation, which forms a hollow evagination of the brain-roof—the *pineal*

<sup>1</sup> The epiphysis of the mammal was known to the ancient Greek anatomists. Galenus described it as the "Σῶμα κωνοειδές, Κωνάριον." Descartes, in 1649, as is well known, considered it to be the seat of the soul.

*process.* The distal extremity of this pineal process becomes enlarged to a sac-like structure, which subsequently becomes lobed and solid. This is the *pineal body*. The proximal part of the evagination remains hollow, and forms the *pineal stalk*, and the whole structure, body and stalk, is usually called the *epiphysis* [McMurrich (30)].

In the Reptilia and other lower groups of animals the outgrowth from the roof of the diencephalon is double, a secondary outgrowth arising from the base or from the anterior wall of the primary one. This secondary outgrowth—the anterior evagination—becomes elongated until it reaches the epidermis of the head, and here it develops into the *pineal eye*. In mammals this anterior process is not developed.

In addition to the epiphysial evagination another evagination arises from the roof-plate of the first cerebral vesicle. This is placed farther forward in the region which subsequently becomes the median portion of the telencephalon. This structure is called the *paraphysis*, and is found in the lower vertebrates and in the marsupials [Seleuka (37)], but up to the present time has not been found in other groups of the Mammalia. It is supposed to be comparable to a choroid plexus which is evaginated from the brain surface instead of being invaginated, as is usually the case. There is no evidence that a paraphysis is developed in the human brain [McMurrich (30)].

#### Histological Structure of the Pineal Body.

The pineal body is covered on its upper surface by the pia mater, which provides the connective-tissue skeleton of the organ, and carries the bloodvessels into the interior. This sheath of connective tissue sends in septa, which break up into a fine network in the parenchyma of the gland, and divide up the whole structure into "acini," or "follicles" [Faivre (12), Stieda (38), Hagemann (21), Henle (23)].

Some writers [Bizzozero (3, 4), Dimitrova (8)] state that there are no true septa, but irregular trabeculae. It seems that in regard to the distribution of the connective framework of the pineal body there is considerable difference between different species and between different animals of

the same species, but of different ages. In the connective-tissue cells a yellowish or brownish pigment is frequently found [Bizzozero (3, 15)].

A number of cross-striated muscle fibres may be found in connection with the connective-tissue elements [Nicolas (31), Dimitrova (8)]. The connective-tissue septa and bands carry in numerous bloodvessels and nerves, of which some are doubly contoured.

The cylindrical epithelium of the ependyma not only covers the part of the pineal body which is nearest to the brain ventricle, but lines certain hollow spaces found within the body of the gland itself [Dimitrova (8)]. The majority of these hollow cavities become obliterated by the proliferation of their lining cells.

There appear to be no true nerve cells in the adult mammalian body. It is stated that there are nerve fibres derived from the brain substance as well as sympathetic fibres, which enter, along with the bloodvessels, in the interior of the pineal body.

The parenchyma of the gland is made up of follicles, which, however, are only sharply marked out at the periphery of the organ. The cells of these follicles have sometimes been described as resembling those of adenoid tissue.

An exact description of the constituent cells of the follicles cannot be compiled from the accounts of the various writers upon the subject. It seems clear, however, that the cells are of two chief kinds—neuroglia and secretory cells. The latter are slightly stainable with a large oval granular nucleus. The cell body contains granules, either distributed throughout its substance, or arranged round the periphery. Galeotti (19) described secretory processes in these cells.

The "brain-sand" ("acervulus cerebri") which occurs in certain follicles, has been known from the earliest times. It has not been shown to be of any physiological importance.



FIG. 92.—Section of the pineal gland of the sheep. (Drawn by Mrs. Thompson.)



It is found also in the choroid plexus and in the pia mater of the lobus olfactorius.

Cysts are also found in the pineal body.

Cutore (6) has recently described a structure in the pineal body of the ox which is of doubtful significance. It is a rounded body of variable size in the roof of the dien-



FIG. 93.—A small portion of the pineal gland of the cat, as seen under a high power of the microscope. (Drawn by Mrs. Thompson.)

cephalon. It may exist side by side with the *diaphysis* described by Favaro (13), and it is connected with a very distinct bundle of nerve fibres. This structure, which the author calls "*corpus præpineale*," appears to reach its maximum development in the later fetal stages and the earlier period of extra-uterine life. After this it becomes reduced, and seems to be absent in the adult.

Costantini (5) calls special attention to the granular nature of the pineal cells, and concludes that the pineal body is an internally secreting gland. Similar conclusions have been reached by Galasescu and Urechia (18), who called special attention to the oxyphile cells of the gland.

#### Physiological Experiments upon the Pineal Body.

Cyon (7) in 1903 made extracts from the pineal bodies of the ox and the sheep, and tested their effects upon the heart and bloodvessels when they were injected intravenously. There was no effect upon the blood-pressure. The number of heart-beats was, however, increased, while the excursion was diminished. This is an effect similar to that obtained by stimulation of the true accelerator nerves.

Such are the effects of small doses. With larger doses the heart-beats become stronger and less frequent, and also irregular. There is frequently to be observed the *pulsus bigeminus* and the *pulsus trigeminus*; there is a disturbance of the harmonious co-operation of the inhibitory and accelerator cardiac nerves. With still larger doses there may be a fall of blood-pressure. Cyon con-

cludes that these effects are due to the calcium phosphate and other salts from the concretions of the gland.

Cyon further performed a series of experiments in which the pineal was directly stimulated. The result of such stimulation was a change in the form and position of the gland. This, Cyon thinks, is due to the striated muscle found in the organ. The experiments were performed upon rabbits. According to Cyon, these experiments point to a mechanical function on the part of the pineal body: it is suggested that it controls the inflow and outflow of cerebrospinal fluid of the third ventricle. The part played by the pineal body in this regard is likened to that of the thyroid and the pituitary, and all three are concerned in regulating the intracranial pressure.

Howell (24), and Dixon and Halliburton<sup>1</sup> (10), record that extracts of the pineal body, when intravenously injected, give a fall of the blood-pressure.

Extracts of the choroid plexus also bring about a lowering of the blood-pressure [Dixon and Halliburton (9), Kramer (26)].

These facts, as also the similar ones, published by Cyon, are probably without any physiological significance, so that we must turn to some other line of observation in order to obtain any light on the function of the pineal body.

A series of extirpation experiments upon the pineal body has recently been carried out by Exner and Boese (11). The authors destroyed, by means of the thermo-cautery, the pineal body in ninety-five rabbits. Of the ninety-five animals, 75 per cent. died within the first twelve hours from bleeding into the ventricle. Twenty-two animals were observed for some time. In six animals the operation was proved to be complete, and they lived to sexual maturity. There was no influence in the direction of premature maturity. The conclusion drawn by these authors from their experiments is that extirpation of the pineal gland in rabbits, if the first twenty-four hours be passed, can be borne without serious consequences, and that in this class of animals, at any rate, extirpation of the pineal gland produces

<sup>1</sup> In reference to these experiments of Dixon and Halliburton, Kidd (25) calls attention to the work of Marburg (27, 28, 29, see below), and suggests that extracts from glands of young animals should be tested.

no noticeable effects. So far as the effect upon adult animals is concerned, Biedl (2) reports similar results, but the effects upon young animals are still in process of investigation.

#### **Pathological Anatomy and Clinical Pathology.**

*Cysts* of the pineal have been known for a long time. Some of these are without characteristic effects ; others give rise to serious symptoms.

*Teratomata* are very common. They were first fully described by Weigert (39), and have since received a considerable amount of attention [Askanazy (1), Marburg (27, 28, 29)].

Various other tumours of the pineal body have been described, such as glioma, sarcoma, carcinoma, and mixed growths.

There is now a general agreement among clinical pathologists that diseases of the pineal body are accompanied by a characteristic train of symptoms. It is curious that there is some degree of resemblance between these symptoms and those due to lesions of the pituitary body.

Our information upon the clinical symptoms in pineal disease is largely derived from the work of Marburg (27, 28, 29).

Hempel (22) records a case of carcinoma of the pineal gland in which there was at the commencement obesity, but later very marked atrophy of the fatty tissues. In complete destruction of the body, which occurred in six cases of malignant tumour, there was a severe disturbance of the trophic functions [Biedl (2)].

Marburg found a very striking obesity in a nine-year-old girl who had the symptoms of a brain tumour. At the post-mortem examination a compound tumour of the pineal body was found. It is not certain whether the obesity is due to a hyper- or to a hypo-function of the gland. Marburg is inclined to the former view, but the preponderance of evidence is, perhaps, in favour of the latter [Biedl (2)].

But there are other interesting conditions besides obesity found in patients with pineal tumours. These are found in young subjects. For our knowledge on this subject we are indebted to Ogle (33), Gutzeit (20), Oestreich-Slawyk (32),

and Frankl-Hochwart (17). These authors have found that in young subjects (boys under seven years of age) symptoms of brain tumour and disease of the corpora quadrigemina are associated with abnormal tallness, unwonted growth of hair, premature sexual and genital development, and early maturity. In these cases there is frequently found on post-mortem examination a teratoma of the pineal body. The symptoms just enumerated are generally supposed to be due to a hypofunction of the pineal gland. Frankl-Hochwart has quite recently (16) published a further account of such cases, and urged the importance of the symptoms mentioned as diagnostic of pineal tumours.

Pellizi (35) has described the pineal syndroma as "macro-genitosomia præcox." There is a premature development of the genitals, which, particularly in regard to the volume of the penis, gives the appearance of an adult. The degree of development of the body and of the skeleton corresponds to that of an age five, ten, or twelve years more advanced. There is a premature ossification of the bones. The intelligence almost always corresponds to the age. In these cases one observes very frequently that there are symptoms of cerebral tumour and destruction of the corpora quadrigemina. The condition always becomes developed before the eighth year, and very frequently before the third, and is commoner in boys than in girls. The hereditary factor has no special influence on the causation. The pathogenesis seems to depend in most cases on a destructive lesion or growth of the pineal body.<sup>1</sup>

<sup>1</sup> Other recent papers on the pathology of the pineal body are : Pappenheim (34), and Raymond and Claude (36). On the histology of the pineal body, see Sarteschi (*Folia Neuro-Biologica*, vi., 1910, No. 6), and on tumours of the body, Bailey and Jelliffe (*New York Med. Journ.*, January 13, 1912, p. 95.)



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## II

### ADRENAL BODIES (CHAPTER XI.).

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## IV

## THYROID AND PARATHYROIDS (CHAPTER XIII.)

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## VII

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