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LECTURES ON THE NERVOUS AND CHEMICAL REGULATORS OF METABOLISM

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THE NERVOUS AND CHEMICAL REGULATORS OF METABOLISM

LECTURES

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BY

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PREFACE

The progress of every science and of every branch of a science is like that of a ship beating to windward, now to one side now to the other of the straight line towards the port ahead, and, every now and then, it is well that the position, as regards the true course, should be determined.

In the study of the regulation of metabolism we have for some considerable time been sailing steadily on the tack of chemical regulation, and it behoves us to consider what point we have reached, and how we lie as regards the true line of advance. This is the object of these lectures.

The advantage, or disadvantage, of such lectures is that the teacher is not only called upon to put forward evidence, but also to assist his student in forming an opinion, by some expression of the views to which he has himself been led. Further, he is, I think, required to consider, not merely the obvious and definite conclusions which can be directly drawn from the observations recorded, but also the probable further significance of such observation. In this way alone can any forecast of progress be made; and such forecasts are in no way dangerous if their purely tentative character is kept in mind. They, at least, stimulate thought and discussion on future lines of work.

I desire to acknowledge my indebtedness to Biedl's[1] *Innere Sekretion.* Students who wish to prosecute further the study of the endocrinous structures will find it invaluable.

Biedl gives so complete a bibliography that I have not considered it necessary to burden the present work with more than a comparatively short list of the more important books and papers, as far as possible in English, and with references to certain papers which I have used in support of some of the theories I have ventured to advance. Such a list, indicating as it does where various illustrations may be found, and the excellent figures in the modern text-books of Histology, obviate the necessity of illustrations in this book. The lectures, when delivered, were illustrated by lantern slides and by experimental demonstrations. Instead of preserving the division into lectures, a sub-division according to subjects has been adopted, and this is so clearly indicated by the use of head-lines and of heavy type in the text that an Index has been considered superfluous.

I desire to thank Dr. E. P. Cathcart for his kindness in reading and correcting proofs.

[1] An English translation of the first edition has been published. A much extended second edition is now appearing in German.

CONTENTS

INTRODUCTORY

It is now universally recognised that the chemical changes in protoplasm which constitute its metabolism are the basis of all the phenomena of life, alike of the manifest activities of movement and of the less visible but no less real activities of development, growth and repair. In fact, we no longer look upon protoplasm as a substance ; we now recognise that it is protoplasm only in virtue of its constant cycle of chemical changes. As Michael Foster has put it : "We may speak of protoplasm as a complex substance, but we must strive to realise that what we mean by that is a complex whirl, an intricate dance, of which, what we call chemical composition, histological structure and gross configuration are, so to speak, the figures." As is here so clearly indicated, we now regard not only functional activity but also structure as a result of the chemical changes in protoplasm.

For the life of the organism co-ordination of the metabolism of all the different tissues and organs is necessary, and each advance in physiology emphasises the marvellous perfection of this co-ordination, and demonstrates still more clearly of what vital moment it is in the life of every being. It was perceived by our forefathers only in dim outline, and to them the nervous system seemed the sole connecting link—

> "For if the sinewy threads my brain lets fall
> Through every part
> Can tie these parts, and make me one of all,"

expresses this conception in words written by John Donne early in the seventeenth century.

But as our knowledge has increased it has been found that other factors play their part.

It is the purpose of these lectures to consider the various factors which bring about this co-ordination and regulation, and which thus determine the orderly development of the body in early life, and the harmonious adjustment of the various activities after full development is reached.

Three factors are chiefly concerned:

1. Hereditary Inertia or Inherited Developmental Tendencies.
2. The Nervous System.
3. The Chemical products of various organs, the so-called Internal Secretions.

The first factor is dominant in embryonic life. The two latter become more prominent as development advances, and in the fully formed higher vertebrates they probably entirely displace the first. It is with them that we have chiefly to deal.

As already indicated, the influence of the nervous system has for long been recognised.

But it is curious that only in quite recent times has attention been directed to the chemical regulation. Johannes Müller, it is true, suggested that glands did not only pour a secretion into their ducts, but that they also gave off products into the blood which might act upon the body. Berthold in 1849 transplanted the testes in young cockerels which he had castrated, and demonstrated the development of the sexual characters. He concluded that the testis yields a substance which acts on the growth of the body.

But it was only when Brown-Séquard, on experimental basis much less satisfactory than that of Berthold, reintroduced the idea that various organs yield products which react upon other organs in the body, that physiologists seem to have wakened to the possibility that such chemical regulation may be of importance in the control of metabolism.

Since that time the subject has received very great attention from an ever increasing number of workers, and there seems to be a growing tendency to regard chemical regulation as something quite apart from nervous regulation, to look upon it as something more fundamental, which existed before a nervous system was evolved, and which goes on acting alongside of and independently of that system.

But it is possible that these products of the activity of organs, these internal secretions, exercise their influence not directly on the tissues, but through the nervous system; that, instead of the chemical regulation being an older and more fundamental mechanism than the nervous, it is really a newer one largely developed to facilitate and to regulate the action of nervous adjustment.

The enormous mass of information which has now been collected concerning the internal secretions, their action, mode of production and inter-relations has put us in a position to take a general view of the situation, and to give at least a partial answer to the question of how they are related to the action of the nervous system.

In these lectures the part played by what I venture to call hereditary inertia will be very briefly considered; the influence of the nervous system, more especially as regards its influence on growth and metabolism, will be dealt with; the physiology of the structures yielding internal secretions, and the mode of action of these secretions will be described; and finally the inter-relationship of these structures and their possible reciprocal action with the nervous system will be discussed.

THE REGULATORS OF METABOLISM.

SECTION I.

HEREDITARY INERTIA.

NEWTON's first law of motion, that every particle of matter in the universe continues in a state of rest or of uniform motion in a straight line unless so far as it is acted upon by external force is as applicable to living as to non-living material, and it applies to the course of development and differentiation of the ovum.

Generation after generation, a similar piece of protoplasm, undergoing the same active molecular movements, is placed under the same external conditions, acted upon in the same way from without, and hence it must undergo the same course of development and differentiation which its progenitors have undergone, with, of course, the possibility of alteration in this course as a result of changes in the external conditions. This, I think, we may call Hereditary Inertia—defining Inertia in terms of Newton's first law.

Oliver Wendell Holmes has said that every normal man placed under the same conditions will do the same thing. And in any ovum the process of growth, of division and of differentiation should be the same as in all others. The external conditions may vary within wide limits without necessarily materially acting upon the protoplasmic metabolism, and the inertia of heredity, that is, the law of movement in a straight line, may carry the process onward to complete differentiation and to the consummation of the fully developed organism.

In the earlier stages of development, the influence of these inherited developmental tendencies is fully recognised. So marked is it that when, at a sufficiently early stage, one blastomere is separated from the rest it may undergo the same processes of development and growth as the mass from which it is separated.

In many of the lower vertebrates this power of self-differentiation persists till an advanced stage of growth, as is shown by the researches of Ross-Harrison, Hooker and others upon young tadpoles. All the tissues, and even so complex an organ as the heart, may evolve after the nervous system has been completely removed at a time when the neural canal has just closed, and when presumably no emigration of nerve cells has taken place into the tissues. Not only does structural differentiation occur, but functional activity develops. The normal rhythmic beat of the heart appears, and, although the voluntary muscles do not exhibit spontaneous movements, they are capable of contracting in response to stimulation.

One of the difficulties in determining the part played by the nervous system in controlling the metabolism of growth and development is the impossibility of ascertaining when this hereditary inertia becomes insufficient to carry forward unaided the developmental processes.

SECTION II.

THE NERVOUS SYSTEM.

Development. Very early in the course of development in vertebrates a nervous system makes its appearance. Long before any of the organs are differentiated the neural groove appears down the back of the blastoderm, and soon closes in to form the neural canal.

From this tube of epiblastic cells an emigration of neuroblasts begins to take place almost at once into the differentiating organs, so that, before their component tissues become recognisable, each of the visceral organs is permeated by nerve structures.

Many of these neuroblasts are arrested in their outward course in various ganglia.

In each metamere a massing of these cells occurs to form the ganglion of the posterior root of the spinal nerves—the *spinal ganglion*. From these cells processes grow inwards to the cord and outwards to form dendritic terminations in the skin and other structures.

Other cells, passing out chiefly by way of the posterior roots, but also to a less extent by the anterior roots, are arrested in front of each metamere to form the sympathetic or *lateral ganglia* of the sympathetic chain. They send out processes both towards the viscera and also into the somatopleure to supply the unstriped muscles, blood-vessels and glands.

Some cells wandering further afield come to rest in more remote situations, in *collateral ganglia*, such as the ciliary[1] ganglion behind the eye and the superior and inferior mesenteric ganglia in the abdomen. Others migrate right down into the tissues, there to form the *terminal ganglia*—plexiform networks of cells and fibres, such as Auerbach's and Meissner's plexuses in the intestine, and the ganglia of the heart. The whole series of emigrated cells maintains a connection with the central nervous system, and constitutes the great sympathetic or autonomic system of nerves, a system which, coursing along the blood-vessels, reaches into every part of the body.

This system may be divided into two parts. The first is derived from the spinal roots of the thoracico-abdominal region of the cord, and may for brevity be called the "true" sympathetic system. The second is developed in connection with the nerves leaving the central nervous system at its cranial and sacral parts—at its two extremities—and may be called the "para" sympathetic. The term autonomic

[1] Morphologically it is true that the ciliary ganglion may be of the nature of a lateral rather than a collateral ganglion.

system, given to the latter by German writers, appears to me misleading.

From the cells towards the ventral side of the cord processes grow outwards. Some are linked up to the developing muscle-plates to form the ordinary nerves of the muscles, but others probably become related to the emigrated cells of the sympathetic system.

Influence on Metabolism. In earlier embryonic life the chemical changes, which are the basis of all growth and structural change, are, as already indicated, controlled by hereditary inertia and by the direct influence of changes in the surroundings. But, as the nervous system develops, the changes in environment act more and more through it, so that vital processes are dominated by nerve influences, and become less and less dependent on the factors which previously governed them. At last, in the fully formed animal, all the manifest activities of body, muscular and glandular, somatic and visceral, alike, are controlled and regulated by the highly developed nervous system, the integrative action of which has been so brilliantly elucidated by the work of Sherrington.

To deal with this general co-ordinating action of the nervous system would be to take up practically the whole range of physiology, and we must confine our attention to the question—What part does the nervous system play in the control of these metabolic processes which are the basis of growth and development and repair?

The problem is no easy one. The initial directive influence of hereditary inertia—the "self-differentiating" of the tissues—must be admitted. If the nervous system, as it gradually evolves, comes to play a part in the process of development, a stage must be reached at which both factors are in operation, and at this stage it must prove difficult to distinguish their effects. This, I think, accounts for the very contradictory conclusions arrived at by various investigators of this problem in embryonic amphibia, on which most of the experimental work has been done. It appears to me that the question should first be studied in the adult, where the full influence of the nervous system may be supposed to have developed, and that, if evidence is forthcoming of a direct influence of the nervous system upon metabolism, the investigation may then be carried backwards, not to answer the question, Does the nervous system have this influence? but to ascertain at what time this influence becomes dominant, at what time it replaces the "self-differentiating" action of hereditary inertia. The difficulty, however, arises that, in the adult, growth and development of most of the tissues is completed, and hence the influence of the nervous system upon these processes cannot be directly observed. But the fact that in amphibia regeneration of amputated limbs occurs has been utilised.

A. EVIDENCE FROM REGENERATION.

In the interpretation of the results of such observations many difficulties arise—

1. Destruction of the cord, even when it involves the spinal ganglia, leaves intact the autonomic system.
2. The persistence of hereditary inertia is probably different in different animals, and in some may actually extend on into adult life. Certain it is that in some amphibia regeneration goes on more readily than in others. In the adult frog the power of regeneration is poorly developed, but in one American newt, used by Goldfarb in his experiments, it appears to be very specially marked.

Wolff, in 1895 and 1896, recorded experiments upon the development of tadpoles and upon regeneration of limbs of adult newts. After removal of the part of the spinal cord connected with the limb amputated, regeneration occurred; but, when the spinal ganglia were also removed, regeneration was interfered with.

Barfurth, 1901, got regeneration of the point of the tail of the axolotl when separated from the nervous system. Rubin, 1903, cut all the nerves of the fore limb of axolotl and amputated the fingers or the whole hand, and found that regeneration starts, but that later it is retarded and is incomplete.

Wolff's results were severely criticised by Goldstein, who, however, concerned himself generally with the influence of the nervous system in larval forms. He concludes: "in the stage of 'organ-forming development' (Roux) the developmental progress of regeneration in general advances in full independence of the nervous system. In the stage of 'functional development' for both processes a clearly expressed influence of the central nervous system is present."

Walter repeated Wolff's regeneration experiment on the adult newt, and he concludes that the posterior root fibres have a direct influence on the progress of regeneration. On the other hand, Goldfarb, 1907, after rejecting various amphibia because the results obtained were not satisfactory, selected a newt, *Diemyctylus viridescens*, which is characterised by a very marked power of regeneration, and he states that regeneration went on normally after destruction of the cord and of the spinal ganglia. These results were severely criticised by Walter in a subsequent paper.

Of these conflicting experiments, the most careful and convincing are undoubtedly those of Walter. In these the histological examination was most full and complete.

The result of a study of the work done is to leave the impression that the nervous system, and more especially the spinal ganglia, have a direct influence on the process of regeneration. Even if the results of Goldfarb are accepted, they by no means exclude the influence of nervous tissue in the great sympathetic system which was left intact.

With the large series of experimental investigations upon the effects of removal of the central nervous system in larval amphibia, we need not concern ourselves further than we have already done. As already pointed out, the undoubted persistence of the influence of hereditary inertia and the possible blending of this with the influence of the nervous system at this stage makes the interpretation of results most difficult, and of little value in the solution of the question, To what extent does the nervous system dominate the metabolism?

One interesting set of observations by Dürken may be referred to. He shows that in young tadpoles there is a marked co-relation between the "Anlage" of the limbs and the central nervous system, and that removal of one of the limb-buds may be followed by failure in the development in certain definite parts of the nervous system—in peripheral nerves, spinal ganglia, motor cells of the spinal cord and even in the hind and fore brain. In some cases he finds that destruction of one limb-bud is followed by malformations of others, and that these are also associated with changes in the central nervous system. These results indicate a close co-relationship between the nervous system and the developing tissues, and support the view that the former undoubtedly acts upon the latter and is reacted upon by it.

It is unnecessary to discuss the large series of observations which have been carried out upon regeneration in invertebrate animals. But the recent experiments of Morguli upon ophiurid starfish may be referred to as showing the influence of nerves even in such simple forms of life. He found that regeneration of the rays did not occur when the nerve was removed from the amputation wound, but that if the nerve was left, even although it had been separated from the central ring, regeneration occurred. This regeneration was less marked when the connection of the ganglionated ray nerve with the central ring had been divided.

Herbst's well-known experiment on the regeneration of the eye of *Palinurus vulgaris* also shows the important influence of nerve in regeneration in invertebrates. When the eye was simply removed it regenerated completely; but when the stem with the eye ganglion was also removed, the regeneration resulted in the formation of an antennule instead of an eye.

The conclusion seems justified that at some stage of development, which varies in different animals, the nervous system comes to have a direct and important action upon the processes of growth and development.

B. GENERAL EVIDENCE.

A. Influence of Central Nervous System. In many animals, apart from regeneration, there is direct evidence of the influence of the central nervous system, not only upon the rapid metabolism of muscle, which is the basis of its contraction, but also upon the slow nutritional chemical changes which maintain its growth and repair. Section of the anterior roots of spinal nerves leads to paralysis of the muscles supplied and to progressive atrophy. It is true that the nutritional chemical changes can be maintained by appropriate electrical stimulation applied directly to the muscle, but this in no sense disproves the action of nerve when it is intact. It is a substitute for that action.

As regards other tissues there is a good deal of evidence which requires examination.

In 1823 Herbert Mayo described inflammation and ulceration in the eye following upon section of the fifth cranial nerve. These results were confirmed by Magendie in 1824, and by Bernard in 1868. They have been ascribed to the influence of external irritants which are not removed on account of the loss of sensation. But that this is not the whole explanation was proved by Sinitzen in 1871. He then showed that the ulcerative changes in the eye produced by section of the fifth nerve may be prevented by removal, a short time before, of the superior cervical ganglion which leads to hyperæmia of the eye. His results were confirmed in 1894 by Spallitta.

Baldi (quoted by Luciani) in 1889 cut the posterior and anterior roots of the nerves to the fore and hind legs of dogs. In both limbs he got a transient hyperæmia of the skin disappearing in a few days, erosion of the claws, loss of hair and excoriations on the skin. The limb had to be kept bandaged to prevent extensive ulceration. When the hair was shaved on the back of the foot it took twice as long to grow as in the normal limb, and was less developed. When croton oil was applied, the vesicles formed twenty-four hours later than in the normal limb, and the new epidermis appeared fourteen days later. That these results were not due to paralysis of motion and sensation he proved by cutting the spinal cord, when no trophic changes appeared.

Clara Jacobson, working under Carlson, cut the posterior and anterior nerve roots in the lumbar region of pigeons on both sides, and found that wounds in the paralysed area healed as well as those on the normal side. Carlson and Werelius cut the dorsal cutaneous rami in three contiguous spinal nerves in three dogs, and the posterior roots in three other cases, and found that healing of wounds and growth of hair were not interfered with. Obviously more work upon this question is required.

As regards glands, Bidder states that section of the nerves to the salivary glands brings about a decrease in their size to one-half.

Nélaton, from clinical experience, concluded that section of the nervi spermatici caused atrophy of the testis. Obolensky showed by experiments upon animals that after section of these nerves the testis became distinctly smaller in two or three weeks, and that after four weeks it had almost disappeared.

Section of the vas deferens did not produce this effect.

The evidence of pathology also points to the direct influence of the nervous system, not only upon the muscles but also upon the connective tissues, bone and epidermis.

In infantile paralysis, acute *anterior poliomyelitis*, where the cells of the anterior horn of grey matter are affected, not only does atrophy of the muscles of the limb occur, but the bones and connective tissues stop growing, and the limb remains small. A curious point is that the growth of the bones in length is much less interfered with than their growth in thickness. This decreased growth is sometimes ascribed to the absence of the stimulus of muscular contraction. Such muscular contraction can act upon the growth of bone only by modifying its blood supply, and this it must do through the nervous reflex arc. Such trophic disturbances of bone are not only seen in children, but they may occur in hemiplegia in adults. Purves Stewart states that the bones may become very brittle, so that fractures are readily caused. The interest of these changes in the bones through the influence of the nervous system will be made more manifest when the effects of some of the internal secretions are being considered.

Evidence is also afforded by the somewhat rare cases of progressive facial hemiatrophy in which all the tissues of one side of the face undergo advancing decrease in bulk.

But the best examples of the trophic influence of the nervous system is afforded in diseases which involve the posterior roots of the spinal nerves. In *tabes dorsalis* a whole series of trophic disturbances occur. The skin may show peculiar symmetrical perforating ulcers or loss of hair over definite areas. The joints may undergo enormous thickening and distortion in the so-called arthropathies. Similar changes are seen in *syringo-myelia*, a disease in which cavities exist in the spinal cord, with increase of neuroglia and disappearance of nervous elements. In both diseases the bones may become brittle and be easily fractured.

Herpes zoster, a vascular disturbance of the skin along the area of certain nerves, has been definitely associated with inflammatory conditions of the nerve ganglia—the Gasserian ganglion of the fifth when it occurs in the face, and the spinal ganglia when it occurs on the side of the thorax.

The importance of the posterior root fibres and their ganglia upon nutrition is strongly indicated by these facts, and they strengthen the conclusions arrived at by Wolff and Walter from their experimental work upon amphibia (p. 12). This conclusion is further supported by a study of certain monstrosities. Children are occasionally born without a brain or a spinal cord, and yet with perfect development of the trunk and limbs. In such cases the posterior nerve roots have been found to exist with their ganglia upon them, and the sympathetic nervous system has been fully developed. Such monsters seem to be much in the condition of the newts with the spinal cord destroyed, but with the spinal ganglia intact, which have been already described.

There is also some direct physiological evidence as to the importance of these ganglia. Stricker and Morat found that stimulation of the posterior roots induces dilatation of the blood-vessels. These observations were confirmed and extended by Bayliss. Ninian Bruce, working under Hans Meyer, found that croton oil applied to the conjunctiva or skin causes vaso-dilatation, even when the posterior roots of the spinal nerves are cut above the ganglion, but, if they are cut below the ganglion and time for degeneration allowed, no reaction occurs. The application of a local anæsthetic, such as cocaine, also abolishes the reaction. This seems to indicate the existence of a controlling mechanism in these ganglia, although Bruce tries to explain the results on the hypothesis of a forking of fibres beyond the ganglion, thus bringing the results into accord with the post-ganglionic axon-reflex view of Langley.

These facts seem to throw important light upon the way in which, even in cases of total absence of the spinal cord, either developmental or experimentally produced, the nutrition of the tissues may be maintained if the posterior nerve roots are intact. It seems unnecessary to assume with Bayliss the passage of the impulses in both directions along the same nerve fibres. Dogiel has shown the existence of different types of cell in the posterior root ganglia, and possibly different types of fibres, outgoing as well as ingoing, may exist.

B. Influence of the Autonomic System. As regards the influence of the Autonomic System, apart from the central nervous system, evidence of independent action upon the tissues is conclusive only as regards the peripheral or *terminal plexuses.*

1. In the alimentary canal the plexus of Auerbach has been shown by Bayliss and Starling to preside over the peristaltic movements of the intestine, while the more recent work of Magnus indicates that even the swaying movements, formerly regarded as purely muscular in origin, are really dependent upon the plexus.

The onset of rhythmic contractions in the heart, before nerve structures can be detected in the organ, has led many observers to conclude that both the onset and spread of the contraction is purely a function of muscle. But the most recent work upon the existence of nervous elements in the auricular walls and in close association with the sino-auricular node, and the indications we possess of the function of that structure in dominating the cardiac rhythm, indicate that these terminal ganglionic structures probably have a direct action.

The existence of peripheral plexuses in the walls of blood-vessels has been clearly demonstrated by the investigations of Dogiel, and their presence explains many of the phenomena of local control after section of nerves.

In the bladder, the demonstration by Goltz and Ewald that, after removal of the lumbo-sacral part of the cord in the dog, the function of the organ, although abolished for a time, is partially restored, so that urine can be retained and evacuated under local stimulation ; and the observation of von Zeissl that section of all the nerves to the bladder does not prevent urine accumulating in the viscus and being periodically expelled, point to the existence of some local nerve mechanism. Lewandowsky and Schultz, it is true, could confirm this result of Zeissl only in bitches, but they admit the existence of sphincter tone. The functions of the bladder involve not merely muscular contraction but co-ordinated contraction and inhibition, comparable with the process of peristalsis in the intestine, which must require the action of some form of nervous mechanism. Griffiths and Stewart both found that, after isolating the hypogastric plexus from its central connections, bladder reflexes could be obtained. Metzner suggests that these may be of the same nature as those described by Langley and Anderson in the inferior mesenteric ganglion as axon reflexes (p. 24). All these investigations seem to indicate a peripheral nervous control from the plexus hypogastricus, if not also from the inferior mesenteric ganglion.

In giving such prominence to these terminal ganglia, I am influenced not only by physiological evidences, but also by W. Abel's work upon the development of the autonomic system, carried out in this laboratory, and by the work of Dogiel. I do not think that any one who has not seen preparations showing the emigration of neuroblasts to form the autonomic system can realise the extent to which it goes on.

The importance of these peripheral plexuses is still further emphasised by recent work upon the nervous mechanism of autonomous organs of invertebrates. Alexandrowicz, working under Biedermann in Jena, and using the methylene blue method, finds that in the heart of such molluscs as the snail and octopus, in the heart, intestine and sex organs of a tunicate (*Ciona intestinalis*) and in the heart and blood-vessels of various decapod crustacea, nerve fibres and nerve cells forming a true plexus are present, and that in the gut of the snail the cells are differentiated into two types—one small, which he supposes to be sensory or receiving; one large, which he suggests as motor.

2. On the mode of action on metabolism of the *collateral ganglia*, such as the ciliary, submaxillary and sublingual, otic, the superior and inferior mesenteric, and the hypogastric ganglia, our knowledge is very imperfect.

François Frank finds that section of the third nerve produces a less marked dilatation of the pupil than does section of the post-ganglionic fibres from the ciliary ganglion, while Jegorow finds that excision of the ganglion produces a greater effect on the pupil than does section of the third nerve. This would indicate a tonic influence of the ganglion upon the dilator pupillæ. P. Schultz failed to confirm this.

Upon the splanchnic nerves and the *plexus solaris* various experiments have been performed by Vogt and by Popielski. It appears that section of the splanchnics causes no marked changes in the intestine or kidneys. Removal of the *plexus solaris*, according to the investigations of Popielski, causes in dogs marked symptoms in the alimentary canal, such as diarrhœa, hæmorrhages, masses of desquamated epithelium in the stools, etc. Such results seem to indicate an influence of the ganglion on the intestine independent of the central nervous system.

Less conclusive are the well-known results of section of the chorda tympani nerve upon the submaxillary and sublingual glands, producing as it does an increased or "paralytic" secretion. This has been ascribed to a stimulation of the submaxillary and sublingual ganglia, and would seem to indicate an action of these structures upon the glands.

The conclusion of Claude Bernard, based upon his experiments on the submaxillary ganglion, that these collateral ganglia are the seat of peripheral reflex action has been discredited by the investigations of Langley and Anderson. One of the best marked of these apparent peripheral reflexes is that described by Sokownin in the bladder. He showed that when the connections of the inferior mesenteric ganglion with the central nervous system were severed, stimulation of the central end of one cut hypogastric nerve caused a contraction of the bladder. Langley and Anderson confirmed this observation, and showed that it did not occur if the ganglion is painted with nicotine. But they found that, if after section of the preganglionic fibres time is given for their degeneration to take place, the reflex can no longer be elicited. From this they conclude that it is not a true reflex but is dependent upon a stimulus passing up the axons of efferent preganglionic fibres which have not been interrupted in the ganglion, but which have given off a collateral to form synapses there. The conclusion as expressed by them is fairly guarded—"On the whole we think that the balance of evidence is distinctly in favour of the view we put forward, viz. that the reflexes obtained by stimulating the central end of the hypogastric are due to nervous impulses which pass up motor fibres and spread to the branches they give off to the ganglia of the opposite side, and so down the opposite hypogastric nerve."

3. The evidence we possess for or against the influence of the *lateral ganglia* of the sympathetic chain is even less satisfactory than that which we have just dealt with as regards the collateral ganglia.

Section of the cervical sympathetic which carries impulses from the spinal cord to the cell stations in the superior cervical ganglion, does not modify the action of adrenalin on the pupil of the cat, but removal of the ganglion with the subsequent degeneration of the post-ganglionic fibres leaves the pupil peculiarly sensitive to the action of adrenalin, so that for some time after dilatation is readily produced. This seems to indicate that the cells of the ganglion exercise a constant action upon the muscle fibres of the iris.

As will be afterwards shown (p. 48), the explanation has been offered that the point upon which adrenalin acts is rendered more sensitive by degeneration of the nerve fibres. But the complete disappearance of peripheral plexuses, after degeneration of the nerve fibres passing to them, has not been proved, and investigations carried on by Pollock in this laboratory seem to show that it does not occur.

Langley, as a result of his extensive and masterly investigations on the autonomic system, concludes (Schäfer's *Text Book*, vol. ii. p. 677, 1900): "On the whole, the evidence at present leads us to conclude that autonomic ganglia, after separation from the central nervous system, do not exercise any considerable tonic action on unstriated muscle, but that it is possible they have a slight action.

"Apart from tonic action, it is not improbable that peripheral nerve cells, severed from the central nervous system, may at times stimulate the tissues to which they send fibres. The nerve cells and fibres remain responsive to chemical and mechanical stimuli, and it is not unlikely that substances circulating in the blood and the movements of the body now and then serve as stimuli to the local nervous mechanism, and so set in action the peripheral apparatus.

"So far we have considered nerve cells which normally exercise a tonic influence on the tissues with which they are in connection. Of the others there is little that need be said here. There is some evidence that the submaxillary ganglion passes into a state of slight tonic activity after section of the chorda tympani, for, so far as the experiments have gone, dyspnœa increases and chloroform decreases the paralytic secretion."

The subsequent work of Bayliss and Starling and of Magnus on the peripheral plexuses of the gut, and the evidence which has been adduced above, all strengthen the view that at least many of the autonomic ganglia do exercise an influence on the metabolism of the tissues they supply.

The elaborate and painstaking work, both anatomical and physiological, of Langley and Anderson, taken along with this more recent work, and with the results of the later investigation on the development of the autonomic system, seems to indicate that there is no essential difference between the various ganglia—lateral, collateral and terminal. The point of arrest of the emigrating neuron cells seems to vary in different species and even in different animals of the same species. Autonomic action appears to be most marked where the terminal plexuses are best developed, as in the wall of the gut, but in all probability the same kind of action is exercised by the more proximal ganglia. It may well be that the axon reflexes of Langley normally play an important part in these actions.

One undoubted purpose of these ganglia is to act as distribution stations for the nervous impulses coming from the central nervous system. With the extensive growth of the alimentary canal, of the

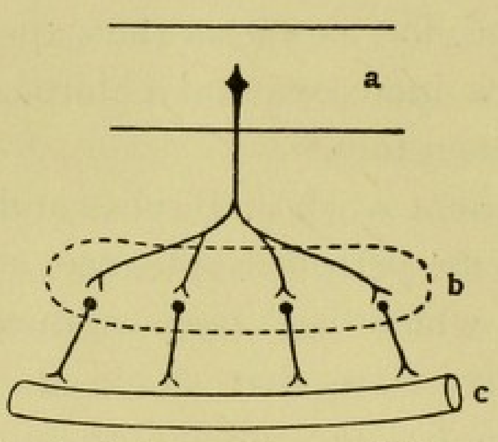


FIG. 1.—To show how, by development of a sympathetic system, the control of a central neuron is extended. The terminal ganglia are omitted.

heart and of the blood-vessels, it becomes of advantage that a small portion of the central nervous system should be able to control a large extent of these visceral structures. This is probably partly effected by one set of preganglionic neurons playing upon many sets of post-ganglionic neurons in each ganglion or series of ganglia as figured by Langley (Fig. 1).

A curious and interesting difference between the innervation of the somatic muscles and those of the viscera is emphasised by Sherrington. In the former, the same outgoing neuron serves for augmentation and inhibition, whereas in the latter, separate neurons, one set causing augmentation, another set causing inhibition, pass to the peripheral structures. If the peripheral structure upon which these neurons play is the terminal nerve plexus, then we have to regard this plexus as the homologue of the motor neuron of the cord, possibly of the spinal reflex arc. Sherrington's work most clearly shows that it is neurons in the cord which act as augmentors or inhibitors on the neurons to the skeletal muscles, and hence they may be regarded as the homologues of the autonomic nerve fibres. But, since precision and not diffusion of action is required, they need not be complicated by the development of distribution stations similar to those in the sympathetic ganglia, and such ganglia are absent.

This conception of the relations of the two mechanisms may be diagrammatically represented as follows (Fig. 2).

I have purposely refrained from the use of the term "Trophic Nerve," because it appears to me that all nerves which modify the metabolism and so the activity of a structure are necessarily trophic, and that no nerves which do not thus modify metabolism can have a trophic or any other influence. The discussion by von Tschermack in the *Folio Neurobiologica*, Bd. 3, p. 676, 1910, on the existence of such nerves seems to me beside the mark. The evidence he adduces is simply for the influence of nerves upon metabolism, not for the existence of special trophic nerves.

Modes of Action of the Nervous System. Accepting the evidence that the nervous system does modify

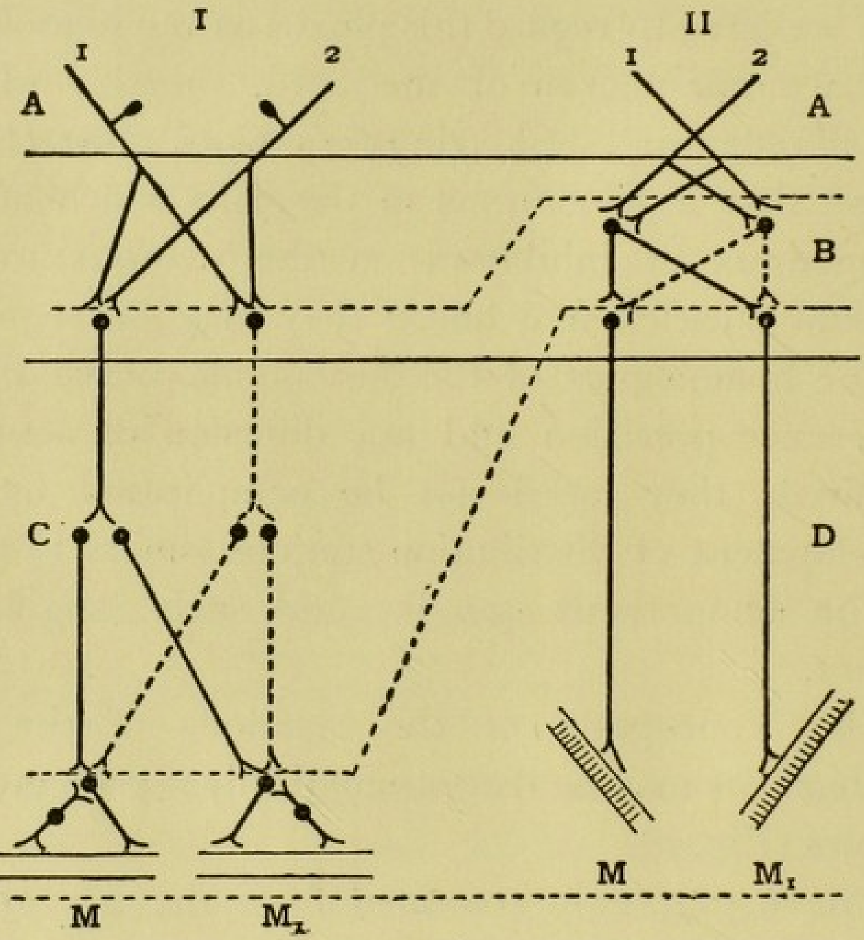


FIG. 2.—To show the homologies between the various parts of the innervation (I.) of visceral and (II.) of skeletal muscle. A 1 and 2. two afferent neurons, stimulation of each leading to a definite augmentor and inhibitory result in the muscles supplied M and M_1. B. The intercalated neurons resolving the stimulus into augmentor (uniform line) and inhibitory (dotted line) effects. C. The distributive ganglia of the sympathetic system not represented in the innervation of the skeletal muscles. D. The efferent nerves to skeletal muscles and the terminal ganglia in visceral muscle with which they correspond.

and control the metabolism upon which development and growth depend, the ways in which this control is exercised may now be considered.

The influence of efferent nerves upon growth and development may be either direct upon the living cells of the tissues, or indirect by their action through the blood-vessels. Although evidence may be wanting of an increase of metabolism as the result of an increased blood supply, there is undoubted proof—*e.g.* that afforded by the development of adipose tissue—that the cells can take up an increased amount of nourishment when that is supplied, and that, if the supply of nourishment is cut off by constriction of vessels, decreased growth and even death may ensue. And, further, the action of ergot in bringing about a contraction of the peripheral vessels and, as a result, death and necrosis of the comb and legs of fowls indicates the great importance of the nervous control of blood-vessels upon nutrition.

Ingoing nerves may react reflexly upon tissues in the same directions.

The suggestive work of Gaskell on the mode of action of inhibitory nerves cannot be ignored in any consideration of the influence of the nervous system on metabolism. Accepting the negative variation of the current of injury in the heart as indicative of increased catabolism in the contracting part, he investigated the effect of stimulation of the vagus and found that, during the inhibition, the current of injury was increased. From this he argued that the anabolic processes are increased, and he classified nerves into catabolic and anabolic.

The important influence of the nervous system *upon development, growth and nutrition is thus established.* But the period of development at which it becomes prominent and replaces the primary adjustments, generally described as "self-differentiation," probably varies in different animals and in different tissues of the same animal.

In thus recognising the part played by nerve, it must, of course, be borne in mind that tissue growth may go on independently of nerve influence. This is clearly shown by the persistence and growth of grafts of various organs in the animal body, when, so far as we know, only the ingrowing blood-vessels carry nerves with them. It is also shown by the recent interesting experiments of Ross Harrison, Carrel and others on the growth of tissues in a suitable nutrient medium *in vitro*. But the question of co-ordination with other structures is not here involved, and such observations in no way invalidate the conclusion as to the important part played by the nervous system as a regulator of metabolism.

Summary. A consideration of the evidence as regards the influence of hereditary inertia and of the nervous system upon development, growth and repair has led us to the conclusion that, while in early embryonic life the former is prepotent and is itself sufficient to explain the self-differentiation of the various tissues and organs, at some stage in development the nervous system comes to play a part in the regulation and co-ordination of the metabolism upon which these processes depend.

The part played by the central nervous system has been seen to be fully established, while the evidence as to the action of the autonomic system, although less conclusive, leaves little doubt that it too exercises an influence.

SECTION III.

THE ENDOCRINOUS GLANDS AND THEIR INTERNAL SECRETIONS.

In addition to the action upon metabolism of hereditary inertia and of the nervous system, which have been considered in the previous sections, the influence of chemical changes also play an important part.

The course of development and of growth may be materially modified not only by artificially modifying the chemical constitution of the fluids surrounding the organism, but also by changes qualitative or quantitative in the metabolic processes of some part or parts of the body. The most striking example of chemical regulation is, perhaps, the effect of the increased production of carbon dioxide by muscle during contraction, leading as it does to increased activity of the nervous structures constituting the respiratory centre, and thus causing the marked augmentation of the respiratory movements which follow upon muscular effort.

But not only may such a general product of metabolism act upon some particular structure or group of structures, but definite and specific chemical products may be elaborated in certain organs and have for their special purpose the modification of the chemical changes in some other organ or organs. In acting in this way they may so control the course of development and growth during early life, and of metabolism during later life, as to bring about a co-ordination between the activities of different organs, and thus to merit the name of *Chemical Regulators.* But it is needless to introduce new terms. These products have already been called the *Internal Secretions,* and the organs producing them have been named the *Ductless Glands*—a misleading title—or, better, the *Endocrinous Glands,* a term indicating that they produce an internal secretion.

Every living tissue probably yields products which may act upon other tissues, but the name endocrinous glands may conveniently be reserved for those structures which yield a product having some definite and specific action, not necessarily of the nature of excitation. Hence the name of Hormone cannot be used to indicate all the internal secretions as some writers use it at present.

These structures may be classified according to their seat of origin into the following groups:

1. *From the Nervous System.*

    Chromaffin Tissue.

    Hypophysis cerebri.

2. *From the Buccal Cavity.*
   Thyroid.
   Pituitary.
3. *From the Intestine.*
   Pancreas.
   Mucosa of Small Intestine.
4. *From the Branchial Arches.*
   Parathyroids.
   Thymus.
5. *From the Mesothelium of the Genital Ridge.*
   Gonads.
   Inter-renal Bodies.

The origin, structure and physiology of these must now be considered.

As development advances, in some cases tissues derived from different sources become closely associated with one another. Thus the chromaffin tissue, formed from the nervous system, in mammals becomes surrounded by the inter-renal tissue developed from the mesothelium of the genital ridge, and they together form a structure generally known as the supra-renal gland. Similarly the hypophysis cerebri becomes associated with the pituitary to form one structure, and the para-thyroids become very closely associated with and even embedded in the thyroid. Even the thymus is possibly a double structure composed of the epithelium of the branchial clefts with masses of lymphocytes infiltrating it.

It has been customary in considering the physiology of these various structures to deal with them according to their anatomical distribution in organs. This seems to me to have led to difficulties and complications, and I shall classify them according to their source.

I. DEVELOPED FROM THE NERVOUS SYSTEM.

I. THE CHROMAFFIN TISSUE.

Development. The chromaffin tissue is derived, with the cells of the sympathetic ganglia, from neuroblasts of the central nervous system which emigrate from the neural tube. Early in embryonic life it extends all along the front of the vertebral column, but in later life it becomes reduced in amount, and in some animals it is more specially associated with the inter-renal tissue, which in mammals forms a cortex around it, thus constituting a supra-renal body.

In fishes the chromaffin tissue remains distinct from the inter-renal tissue.

In birds the medulla is not enclosed in the cortex. It is, in fact, only in mammals that the inclusion is complete.

Even in mammals, subsidiary masses of chromaffin tissue occur outside of the supra-renals, and these are specially well marked in fœtal life, and persist to a greater extent in some species, *e.g.* the rat, than in others.

They are constant at the forking of the carotids, where they form the carotid glands, and at the branching of the aorta.

Structure. The chromaffin cells have this marked peculiarity that, when fully developed, they have a special affinity for chrome salts and so stain of a distinct brownish colour. Hence their name. These cells in the medulla of the supra-renal bodies are collected in masses and columns lying closely upon large sinusoid capillaries. They are destitute of the fat and of the brown pigment which is present in the cells of the cortex.

Physiology. In investigating the physiology of this tissue, the great difficulty is that its main mass in the medulla of the supra-renal bodies, in all higher vertebrates, lies in such close connection with the cortex, a totally distinct tissue. Hence it is practically impossible to separate and to remove the one without interfering with the other. It is true that in elasmobranch fishes they are separate and distinct, a fact which Biedl has taken advantage of in removing the inter-renal tissue (p. 173).

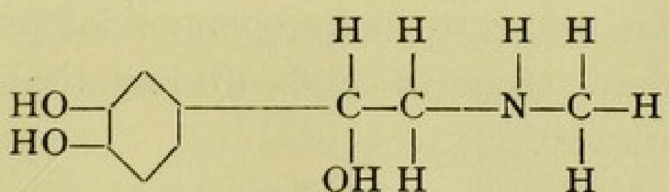
Complete removal of the supra-renals is rapidly fatal. Biedl found that excision of the inter-renal bodies alone is fatal in skates and dog-fish, but whether complete removal of all the chromaffin tissue is compatible with the continuance of life it is at present impossible to say.

In considering the inter-renals it will be found that, while grafting the supra-renals into animals from which they have been removed prevents the onset of death, it has been found impossible by this method to determine the part played by each tissue in maintaining life.

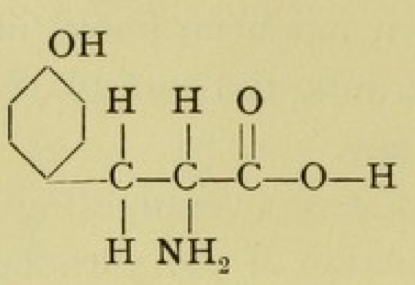
The credit of first investigating by a satisfactory method the function of the chromaffin tissue is due to Oliver and Schäfer, who in 1894 demonstrated that the intra-venous injection of extracts of the supra-renals has a marked effect upon the circulation. Similar results were independently obtained by Cybulski and Szymonowicz, but were published somewhat later.

They found that such extracts, even after boiling, cause a marked rise in the blood pressure due chiefly to constriction of the arterioles, an increased action of the heart and cardiac inhibition if the vagi are intact.

One of the most important steps in the progress of the study of the action of these extracts was the isolation of the active substance by Takamine in 1901. This Adrenalin, as it may best be named, is orthodioxyphenyl-ethanol-methylamine:



It is thus fairly closely related to one of the decomposition products of the proteins—tyrosin or paraoxyphenyl-amino-propionic acid—and its relationship to the protein molecule, of which it must be a derivative, is thus indicated :



That it is a physiological secretion, and not a mere post-mortem product, is clearly demonstrated by many observations in which its well-marked physiological actions are used to investigate its presence and amount. Thus Dreyer and Tscheboksaroff have both shown that stimulation of the splanchnic nerves going to the supra-renals increases the amount of adrenalin in the blood leaving the gland, as indicated by the increased physiological action of the blood of the vein.

Not only has adrenalin been isolated from the supra-renals, but it and various allied products have been prepared synthetically.

The fact that a pure chemical substance is obtainable has thus made it possible to study with great precision the mode of action of this product of the chromaffin tissue, to make commercial preparations of standard strength and to use the substance therapeutically.

It readily becomes oxidised to an oxy-adrenalin, which gives a red colour to the fluids in which it is dissolved. Various oxidising agents, *e.g.* iodine or chlorine water, hasten the change, as was pointed out by Vulpian in his observations on the supra-renals in 1856. He also found that ferric chloride gives a green reaction.

Many chemical tests for adrenalin, chiefly depending upon these reactions, have been devised, but none have proved so reliable or so delicate as the physiological tests depending upon its action on certain tissues.

A colorimetric method described by Folin, Cannon and Denis promises to be sufficiently accurate and delicate for the determination of adrenalin in dilute solution. It depends upon the fact that with phosphotungstic acid adrenalin gives a blue colour even in dilutions of 1 in 3,000,000, while the older chemical methods are sensitive only to 1 in 300,000. As a standard for comparison a solution of uric acid of known strength, 1 mg. of uric acid in 100 c.c., is used, to which is added the same amount of the phosphotungstic and phosphoric acid mixtures with a definite quantity of sodium carbonate, and the colour compared in a colorimeter. This method, checked by the physiological blood pressure method of Elliott, gave strikingly concordant results.

Mode of Action. As already indicated, the first discovered and one of the most prominent actions of adrenalin is upon the **vascular system.** Oliver and Schäfer showed that there is a marked rise of arterial pressure due to constriction of the **arterioles** and a slowing of the heart, unless the vagi are thrown out of action. That the action is a direct one on the blood-vessel walls they demonstrated by perfusing the vessels and so producing the constriction. Later investigations have shown that the arterioles of different regions are affected to very different degrees. Those of the splanchnic region are most markedly acted upon, so markedly indeed that when adrenalin is injected into the general circulation, the blood may be forced from the viscera into the limbs which may actually increase in size from the increased amount of blood in them. Of the visceral vessels, the renal arterioles are constricted first and by the smallest dose of adrenalin.

The intra-cranial vessels are very slightly influenced by adrenalin. The pulmonary vessels are also little acted upon, although Desbouis and Langlois state that large doses constrict and small doses dilate. Hence the intra-venous injection of adrenalin leads to increased pressure in the intra-cranial vessels and to congestion and œdema of the lungs.

The coronary arteries are actually dilated instead of contracted.

The dose necessary to produce a marked rise of blood pressure depends upon whether the vagus is or is not intact. In the former case, much larger doses are required to raise the pressure, since the cardiac inhibition compensates for the vascular constriction. With the vagi out of action, as little as .005 mg. per kilo of body weight, when intra-venously injected, will give a distinct rise of blood pressure in the dog or cat. A dose of .1 mg. per kilo is generally sufficient to give a maximum effect. Below this the extent and duration of the rise is fairly proportionate to the dose. Its duration is always transient, unless a continued perfusion of dilute adrenalin into a vein is maintained.

The action is probably only produced on intravenous injection. Administration by the mouth produces no effect, and subcutaneous injection produces practically none in the dog, cat and rabbit. It is said to raise the pressure in man.

Hoskins and M'Clure find that very small doses of adrenalin give a fall instead of a rise in blood pressure.

This fall in the blood pressure has been recently studied by Cannon and Lyman, and they conclude that it depends largely on the condition of the muscle at the time, and cite the difference in the action of adrenalin on the virgin and on the pregnant uterus in support of this.

The question of whether the action is upon the terminal nerve structures or upon the muscle fibres has been investigated by pharmacological methods. Dixon showed that, after the administration of apocodeine to the extent of producing its curare effect, adrenalin failed to constrict the vessels while barium was still effective. He concluded that while barium must act upon the muscle fibre beyond the plexus, adrenalin acts directly upon the nerve terminations.

In ergotoxin Dale found a substance which, while stimulating in small doses, in large doses has a selective paralysing action upon the motor endings of the true sympathetic, but which leaves the inhibitory endings uninfluenced. He and Elliott found that after ergotoxin stimulation of the splanchnic nerves causes a vaso-dilatation, and that adrenalin acts in the same way. Hence adrenalin stimulates both motor and inhibitory terminations, and its vaso-constrictor action is due to the preponderating action of these constrictor endings in the sympathetic nerves. In the coronary arteries, where these constrictor fibres appear to be absent, adrenalin, as already stated, causes dilatation.

Gunn and Chavasse find that adrenalin constricts the peripheral veins of the sheep after removal from the body and that it causes a rhythmic contraction of the superior vena cava near the heart.

The action of adrenalin on the **heart** is at first sight rather puzzling. With the vagi intact a distinct slowing is produced; but, with the vagi cut out by atropin, acceleration and augmentation occur.

The inhibition is probably reflex through the vagus from the raised arterial pressure.

The augmentation and acceleration which occur when the vagal action is eliminated must be due to some peripheral action, since it occurs in the excised and perfused heart. One of two mechanisms may be involved, the termination of the true sympathetic—the augmentor nerve—or the muscle itself.

Dixon has shown that very large doses of apocodeine paralyse the terminations of the augmentor mechanism, and that after such doses adrenalin fails to augment the heart.

The conclusion seems clear that the terminations of the augmentor nerves are the structures acted upon. On account of this, in mammals, in spite of the high pressure, the ventricular contraction is distinctly increased, since in these the augmentor nerves act upon the ventricles as well as upon the auricles. In birds this is not the case. I find that the action of the augmentor nerves is entirely confined to the auricles, an observation which is fully supported by the beautiful anatomical investigation of Thébault on the vagus and sympathetic in the bird which have only recently come under my notice.

Watson and I showed that in the bird adrenalin causes a marked decrease in ventricular contraction, the increased arterial pressure not being compensated for by the stimulation of an augmentor mechanism in the ventricles.

The law established as to the action of adrenalin on the terminations of the true sympathetic system in the vascular system was shown by Elliott to apply to all parts of the viscera. **Adrenalin produces the same effect as stimulation of the true sympathetic**:[1] when the former causes contraction, the latter also

[1] The term "true sympathetic" is used throughout as equivalent to "abdomino-thoracic sympathetic," while para-sympathetic is used to express "cranio-sacral sympathetic," or what German writers call the autonomic system, a most misleading title.

does so; when it causes dilatation, adrenalin dilates. Hence differences are found in different animals. Elliott has shown, for instance, that the **bladder** of the ferret, which contracts upon stimulation of the hypogastric nerves, also contracts under adrenalin, while the bladder of the cat, which is relaxed by the action of the hypogastrics, is relaxed by adrenalin.

In the **alimentary canal**, where sympathetic stimulation inhibits peristaltic movement, but causes contraction of the pyloric and ileo-cæcal sphincters, adrenalin acts in the same way. Some observations of Hoskins and M'Clure show that it produces this inhibitory action on the bowel in doses smaller than those required to raise the blood pressure.

On the **reproductive** organs, internal and external, the same law applies. An interesting observation made by Cushney and confirmed by others is that, while adrenalin causes contraction of the uterus in the pregnant and recently pregnant cat, it generally causes relaxation in the virgin animal. Stewart's observations on the uterus seem to show that large doses may decrease, while smaller doses may increase contraction.

On the **eye**, stimulation of the cervical sympathetic causes dilatation of the pupil, retraction of the nictitating membrane, contraction of the muscle of Müller—protrusio bulbi—and opening of the eyelids from the contraction of the nonstriped muscle fibres of the lid, and the same effects are produced by adrenalin. The dilatation of the pupil is most readily produced in the excised eye of the frog. Instillation of adrenalin into the eye of mammals—*e.g.* dog, cat and man—does not cause dilatation of the pupil. But Meltzer and Auer found that it did produce the effect after extirpation of the superior cervical ganglion.

This has been explained on the supposition that the sympathetic carries both motor and inhibitory fibres to the dilator pupili, that the latter are thrown out of action by excision of the superior cervical ganglion, and that hence adrenalin makes its action manifest by causing dilatation. The existence of such inhibitory fibres has not been directly proved.

Loewi found that in the diabetes which follows extirpation of the pancreas in dogs, and in some cases of diabetes in man, adrenalin produces a dilatation of the pupil, and he explains this on the supposition that the pancreas stimulates the inhibitory sympathetic nerves (p. 101), and that, only when its effect is removed, can the action of adrenalin on the motor terminations be made manifest. The interest of this observation will be further considered in dealing with the changes in metabolism produced by adrenalin.

It has been found that the response to the action of adrenalin is in many tissues increased after the sympathetic nerve fibres have undergone degeneration. This is well seen in the increased action of adrenalin in bringing about dilatation of the pupil and constriction of the vessels of the ear after the superior cervical ganglion, from the cells of which the post-ganglionic fibres pass, has been excised. Fletcher finds the same condition in the retractor penis after section of all its nerves. A complete denervation of the tissue has been assumed, and Fletcher attempted to demonstrate this by staining with methylene blue. But this method is by no means certain in its results, and the author himself admits that these observations are not satisfactory. The persistence of the peripheral plexuses in the tissues has to be considered. In the iris such ganglionated plexuses have been described and figured by Schock, and Pollock, working in this laboratory, finds that, after complete removal of the ciliary and the superior cervical ganglia of the rabbit leading to complete degeneration of the nerves to the iris, a plexus may still be demonstrated by the methylene blue method. It seems to me that the influence of these "neurons of the third order" have to be considered before it can be safely concluded that an organ is denervated by section of the fibres passing to it.

Metabolism. Blum in 1901 discovered that the subcutaneous administration of adrenalin produced glycosuria.

In 1902 I made the same observation, and independently and in conjunction with Drummond investigated the condition. I found that the glycosuria is associated with a hyper-glycæmia, and that, while it is most marked in rabbits on a carbohydrate diet, it may also be produced in fasting animals even after the carbohydrate store has been depleted by phlorhizin. I also found that it is accompanied by an increased excretion of nitrogen, *i.e.* an increased catabolism of protein, and it thus seemed fair to conclude that not only is the sugar set free from the stored carbohydrates of the body, but that it is also formed from the protein molecule. In fact, one element in the production of the condition is an increased mobilisation of sugar in the body. While glycogen is certainly converted to glucose, its further storage in the liver is not necessarily interfered with. Drummond and I found that, after repeated administration of adrenalin, glycogen was still present in considerable quantities. Pollok describes an actual accumulation of glycogen. He states that in fasting rabbits, and those rendered glycogen free by strychnine, the administration of adrenalin causes an increase of glycogen in the liver, but no increase in the muscles, only traces being found. This may indicate that the production of sugar from proteins has been so great as to leave some available for storage.

The condition can be produced by small doses of adrenalin. I generally used .1 mg. (1 c.c. 1 in 1000) in rabbits, but as little as .01 mg. is said to be efficient. The glycosuria is more readily produced by subcutaneous or by intra-peritoneal than by intra-venous injection, possibly because the last method of administration is apt to check the secretion of urine. Straub and Ritzmann, however, have shown that the continuous inflow of very dilute adrenalin into the blood is sufficient to establish and to maintain a glycosuria. The sugar appears in the urine in less than an hour and lasts for two or three hours. A second dose causes its reappearance. But, after prolonged daily administration, a condition of slight tolerance may be established.

As to how the adrenalin acts, various theories have been advanced. Herter and Wakeman state that direct application to the pancreas produces a powerful effect, and describe the action of other toxic agents when applied directly to the pancreas as causing glycosuria. They thought that it paralyses the pancreas, possibly by constricting its vessels, and that it thus prevents that organ from exercising its checking influence upon the mobilisation of sugar.

I found that removal of the pancreas in birds does not cause glycosuria, but that upon administration of adrenalin to geese and ducks without the pancreas, glycosuria is produced. At that time I did not know of the work of Kausch, who states that, although glycosuria is not readily produced in ducks and geese by removal of the pancreas, hyper-glycæmia does occur. These observations have been confirmed by Fleming in this laboratory. Still, the fact that in my experiments adrenalin increased the glycosuria in the pancreas-less goose is opposed to the view that its only action is upon the pancreas. This conclusion is supported by the observations of Doyen, Morel and Kareff that, in the pancreas-less dog, adrenalin increases the glycæmia, an observation which I have confirmed in diabetes in the human subject. A direct action on the pancreas may then be excluded as the cause of the production of glycæmia.

It would rather seem as if both adrenalin and the internal secretion of the pancreas, which, as will afterwards be shown, checks the mobilisation of sugar, acted at some common point. The surprising generality of the law of the mode of action of adrenalin suggests that this point may be the termination of the true sympathetic in the liver. The work of Doyen and Gautier supports this view. They found that *in vitro* adrenalin had no action upon the conversion of glycogen to glucose in the liver, and that in the living animal, while the injection of adrenalin alone was followed by an increased conversion of glycogen, the previous injection of atropin prevented or decreased this action. This observation should certainly be repeated.

The liver is the great storehouse of sugar as glycogen, and we know that adrenalin produces most marked glycosuria when the store of glycogen is large. Even after the glycogen has been used up, adrenalin still causes a mobilisation of sugar from the proteins, a process which probably also goes on in the liver.

That adrenalin produces this mobilisation of sugar in the liver by acting through the terminations of the true sympathetic system is indicated, not merely by the results of Doyen and Gautier already quoted, but by other evidence. In the first place, a rich plexus of sympathetic origin, derived by migration from the terminal plexus in the gut wall, runs all through the liver. Stimulation of the fibres of the hepatic plexus going to this produces a glycogenolysis, as was indicated first by the brothers Cavazzani, and more recently by M'Leod and Pearce. Again, Miculicich finds that the injection of 2 to 4 mg. of ergotin hinders the onset of glycosuria after the subsequent subcutaneous injection of 1 to 2 mg. of adrenalin, and that the injection of ergotoxin after adrenalin reduces the glycosuria. These results may be due to the well-known effect of ergotoxin in antagonising the action of adrenalin upon sympathetic nerve terminations.

Is the mobilisation of sugar normally caused simply by the action of adrenalin upon these nerve endings?

The observation of Starkenstein that glycæmia and glycosuria may be produced by stimulation of the central end of the vagus after the supra-renals have been removed, shows that direct stimulation through the nervous reflex arc can produce the effect, and that the presence of adrenalin is not essential.

It has been suggested that stimulation of the splanchnics causes glycæmia, not by acting directly upon the liver, but by stimulating the supra-renals to increase their output of adrenalin (see p. 55), and that the adrenalin then acts upon the liver. The question of how far this direct stimulation does increase the output of adrenalin will be presently considered.

But admitting for the time that it does so, an observation of M'Leod and Pearce seems to show that it is not the sole factor. They found that stimulation of the splanchnic nerve did not generally cause glycogenolysis if the hepatic plexus was cut, although it also failed to produce the effects if the supra-renal glands were excised. They, therefore, argued that, while apparently adrenalin in the blood is necessary for the action of the nerves, it is not the direct excitant to the liver. This, of course, does not mean that it cannot, when in sufficient amounts, directly stimulate the nerve endings, but simply that, under normal conditions, its presence is necessary to allow nervous stimulation to act. Its influence might be likened to that of an activator or sensitiser.

These considerations naturally lead to the discussion of the question of what is the relationship of the puncture diabetes of Bernard to adrenalin glycosuria.

A. Meyer showed that puncture diabetes is not produced in rabbits after removal of the supra-renals. Kahn concluded that the puncture brings about a central stimulation propagated down the splanchnics to the supra-renals to increase their output of adrenalin, and this conclusion is supported by the more recent work of Elliott upon the discharge of adrenalin from the chromaffin tissue under the influence of nervous stimulation.

But, while Wattermann and Smit believed that they could demonstrate an increase in the adrenalin in the blood after diabetic puncture, Kahn has failed to confirm their results, although he does not consider that this disproves the outpouring of adrenalin. The evidence at present seems to point to the conclusion that, while puncture of the floor of the fourth ventricle almost certainly increases the output of adrenalin, this increase is not generally so marked as alone to account for the onset of glycosuria, and that probably the stimulation of those fibres of the splanchnic nerves which go to the liver plays a part in bringing about the increased glycogenolysis.

Whether adrenalin, in producing glycosuria, causes any other change in the metabolism of sugar in the body is not definitely known. But the increase in the respiratory quotient observed by Fleming in this laboratory, in ducks, seems to indicate that sugar is used by the tissues, and that in this respect adrenalin glycosuria differs from pancreatic diabetes. This is confirmed by the results of Falta in man. But Wilenko has published a short note of experiments tending to show that under the influence of adrenalin the heart muscle is less able to metabolise sugar. Pancreatic diabetes seems to be something more than a mere adrenalin glycæmia due to an unopposed action after withdrawal of the influence of the pancreas (p. 100).

Adrenalin thus seems to produce all its various effects by stimulating or by sensitising to nervous impulses the terminations of the true sympathetic nervous system.

Influence of Nerves on the Chromaffin System. Is the formation of adrenalin in chromaffin tissue controlled by the nervous system? The medulla of the supra-renals is richly supplied by fibres from the splanchnic sympathetics. Biedl described an increase in the adrenalin content of the blood on stimulating the splanchnics, but pointed out that a vaso-dilator effect is produced upon the supra-renals. Hence only an increased washing out of adrenalin may be indicated. Dreyer had previously described a similar increase in the adrenalin content of the blood on stimulating these nerves, and had concluded that they are secretory in their mode of action. Tscheboksaroff got similar results.

Cannon and De la Paz showed that fright in the cat caused the appearance of an increased amount of adrenalin in the blood of the supra-renal vein.

An elaborate investigation of the question has been made by Elliott, who takes as his index the amount of adrenalin in the gland. He shows that the two glands contain a closely similar amount under normal conditions, and that the emotional disturbance called by him "fright," which in the cat accompanies the administration of morphine and tetra-hydro-β-naphthylamine, is followed by a marked decrease in the adrenalin content of the glands. Section of the splanchnic nerve prevents this discharge. Curiously enough, Elliott did not find that faradic stimulation of the splanchnic caused a marked decrease in the adrenalin content of the gland, although the work of Dreyer and Tscheboksaroff had indicated an increased discharge of adrenalin. On the other hand, stimulation of the central end of an ingoing nerve, such as the sciatic, decreased the adrenalin content of the glands unless the splanchnic nerve had been cut, in which case the gland was not acted upon. Direct injury and stimulation of the brain acted in the same way. The evidence thus clearly points to the existence of a reflex nervous control of the discharge of adrenalin from the medulla of the supra-renal, but whether this is a true secretory action, which actually modifies the production of adrenalin, is not indicated.

But Elliott points out that, important as the reflex control probably is, it is not essential for the continued action of the chromaffin tissue, since a cat, with one supra-renal removed and with the splanchnic on the opposite side divided, does not die till the second supra-renal is removed. The results of Haberer and Stoerk upon grafts afford similar evidence. But this may simply mean that the animal can continue to live without the action of the chromaffin tissue of the supra-renals.

Asher excluded, by removal and ligature, all the abdominal viscera from the circulation except the supra-renals, and found that stimulation of the splanchnics causes a rise of blood pressure. This does not occur if the supra-renal veins are ligatured. The rise of pressure does not occur for about thirty seconds, and it takes place even when the spinal cord is cut across high up. Evidently the stimulation has caused an increased output of adrenalin.

He is unable to confirm the observation of Stahl and Weiss, that a fall of the blood pressure occurs on clamping the supra-renal vein, and in this he is supported by Kahn and by Hoskins and M'Clure.

What is the Physiological Significance of Adrenalin in the Blood? Dixon has advanced the theory that the reaction to stimulation of the true sympathetic system may be due to a liberation of adrenalin in the nerve terminations, and that the chromaffin tissue is a special development of such terminal structures in which adrenalin accumulates. The suggestion is ingenious but lacks proof, and the fact that the nervous response occurs so rapidly is perhaps opposed to it.

That adrenalin is present in the blood has been shown by the use of various physiological methods. Fraenkel estimates that the amount in normal blood is about 1 in 500 millions. According to the results of Fraenkel and of Ehrmann 1 in 20 millions is required to produce manifest effects. In a small dog the injection of about .005 mg. is generally necessary to produce a rise of blood pressure, and this amount diluted with the 1000 c.c. of blood in the animal would give about 1 in 20 millions.

Janeway and Park, testing the presence of adrenalin by its action on a strip of peripheral and a strip of coronary artery (see p. 62), found that 1 in 20 millions of blood or 1 in 50 millions of Locke's solution gave a positive reaction with both preparations. But they entirely failed to get any result with peripheral blood, although they sometimes got a constrictor substance for both vessels. This, according to them, cannot be adrenalin, and hence they conclude that adrenalin cannot be present in the blood in sufficient amount to produce its stimulating effect.

Another method of ascertaining how much adrenalin may be present in the blood, is to determine the amount in the blood of the adrenal vein, and to try to ascertain how much blood flows from the gland. Hoskins and M'Clure have recently attempted to do this, and conclude that in the dog about .25 c.c. of a 1 in 1 million adrenalin may leave the gland per minute. The results of O'Connor in the rabbit give about .2 c.c. This amount is wholly insufficient to influence the blood pressure. Hoskins and M'Clure further argue that since .4 c.c. of 1 in 500,000 adrenalin is necessary to produce an initial effect on the blood pressure, while a *difference* of .1 c.c. of the same strength will produce a *difference* in effect, the amount of adrenalin normally present in the blood is quite insufficient to influence blood pressure. In a more recent paper they point out that the adrenalin produced is only about one-quarter of what is required to influence the blood pressure, and that increasing the amount by continuous inflow into a vein leads first to a fall of pressure, and that five times the amount required to produce the primary depression is necessary to cause a minimum sustained rise. They, therefore, argue that the amount of adrenalin produced is only one-twentieth of that required to give a pressor effect. They further show that before the pressor effect is produced the paralysing influence on the gut is manifest. This seems to indicate that the adrenalin normally in the blood can play no part in maintaining the tone of the vessels.

Their conclusion is that the relationship between adrenalin and the sympathetic system is merely a means of promoting muscular efficiency in times of stress.

But the results of Dreyer, and more especially of Elliott, seem to show that the percentage in the blood may be increased by reflex stimulation, and the question arises—Is the increased outpouring in order to bring about a direct stimulation of the peripheral terminations of the sympathetic nerves or merely so to activate them that the one which is being played upon by nerve impulses may more markedly respond? Is the adrenalin in the blood a stimulator or a sensitiser?

There seems some evidence that, under powerful reflex stimulation, a generalised excitation of all the endings of the sympathetic system may be produced. In the excitation accompanying such emotional disturbances as fear, the erection of the hairs, the dilatation of the pupils, the prominent eyeballs, the pallor and the acceleration of the heart suggest a generalised action, but they do not demonstrate whether this is a general stimulation by adrenalin or a general activation to the influence of an exaggerated nervous outflow.

Under ordinary conditions the amount of adrenalin in the blood is so small that its action seems more probably that of an activator than of a direct stimulator.

In this connection some recent work of von Anrep is of interest. His results tend to show that in stimulation of the splanchnic nerves the initial rise of blood pressure is due directly to the influence of vaso-constrictor fibres upon blood-vessels, but that a secondary constriction is due to the stimulation of the supra-renals and to the increased outpouring of adrenalin. Whether this simply activates the sympathetic terminations or whether it acts directly as a stimulant is not shown, although a second paper on "Local Vascular Reactions" tends at first sight to support the latter view, in as much as it shows a constriction of vessels in denervated limbs when the nerves are not stimulated. But the amount given was greater than that which is found in the blood, and no one denies that in sufficient quantities adrenalin does stimulate directly.

The recent work of Hoskins and M'Clure, of Stewart and of others, showing that the action of adrenalin in small doses may be the reverse of that in such large doses as are generally used in studying its action, tells markedly against the idea that adrenalin in the blood is a direct excitor of the nerve endings.

The evidence seems to show that the initial effect of any activity of the autonomic system is apart from the influence of adrenalin, but that if the action is to be sustained it is accompanied by an outpouring of adrenalin which must fortify the nervous effect either by making the endings more sensitive—by activating—or by replacing and superseding this effect—by directly stimulating. The fact that the nervous effects under normal conditions remain definite and limited tells against the latter hypothesis.

Physiological Methods of detecting and determining the Amount of Adrenalin present. Various methods have been devised, depending upon the relationship of the physiological effect to the percentage of adrenalin.

The most satisfactory of these are—

1st. The Meltzer-Ehrmann Method, depending upon the action of adrenalin in dilating the pupil of the enucleated eye of the frog. It is stated that 1 in 20 million is sufficient to produce the effect.

2nd. Action on the blood pressure in atropinised rabbits. Dr. J. D. Cameron, working under my directions, investigated various methods of testing for adrenalin, and came to the conclusion that the most satisfactory is that of determining the effect upon the blood pressure of the rabbit previously atropinised. She found that in this way .0003 mg. per kilo of animal could be detected. Taking the blood volume of the rabbit at 1/20 of its body weight, and supposing the dose of adrenalin uniformly distributed, this would give .6 mg. in a million, or 1 part in 160 millions. She further found that adrenalin preparations may be standardised against a known dose of nitroglycerine, and that this gives the most reliable results.

A modification of this method, using a pithed rabbit, was employed by Elliott.

3rd. Fraenkel uses the excised uterus of the rabbit in Ringer's solution with a stream of oxygen as devised by Magnus for the gut. The uterus is attached to a recording lever. The introduction of adrenalin increases and alters the character of the contractions. The presence of 1 in 20 or 30 millions may be detected by this method.

4th. Hoskins uses a loop of rabbit's intestine in oxygenated Ringer's solution, and finds that the movements are inhibited by adrenalin. This may occur with 1 in 400 million.

5th. Janeway and Park use (*a*) a strip of a peripheral artery which is constricted by adrenalin, and (*b*) a strip of coronary artery which is relaxed by the substance, each in blood or Locke's solution. Taking the contraction of the former and relaxation of the latter as their index, they find that 1 part of adrenalin in 20 millions of blood and 1 in 50 millions of Locke's solution may be detected.

Toxic Action of Adrenalin. In large doses adrenalin may cause rapid death with cardiac inhibition. The onset of death may be delayed for some minutes —the respirations being quickened and panting. In these cases congestion and œdema of the lungs is marked, while a desquamation of the epithelial lining of the vesicles is also to be seen (Drummond).

In more chronic poisoning a necrosis of the liver tissue was observed by Drummond.

Prolonged administration leads to a degenerative atheromatous change in the walls of the arteries. How far this is a result of the increased pressure is not clearly demonstrated. But the fact that subcutaneous administration causes atheroma, but does not cause increase of arterial pressure, is opposed to the idea that the action is a mechanical one, and suggests that it may be secondary to changes in the arterioles of the vessel wall.

Summary. In this section we have dealt with the origin of chromaffin tissue from neuroblasts similar to those forming the sympathetic nervous system, and with the production of a specific product, adrenalin.

It has been shown that adrenalin has a definite action in stimulating the terminations of the "true" (thoracico-abdominal) sympathetic system, and that not only its action upon the blood-vessels, heart and other muscular structures, but also its effect upon the metabolism of carbohydrates is to be explained in terms of this selective action.

Whether the adrenalin in the blood under normal conditions actually stimulates the terminations, or whether it merely sensitises them to the influence of nerve impulses, or whether it has a secondary action in fortifying the effect of the acting nerve, has been discussed.

II. HYPOPHYSIS CEREBRI.

Development. The hypophysis, like the chromaffin tissue, is derived from the nervous system.

It is formed by a hollow downgrowth from the fore brain in the floor of the third ventricle. In some animals, such as the cat, it remains hollow, but in others, man, monkey, etc., the lumen is closed by the approximation of the walls, and a solid stalk is thus produced. The terminal portion develops a somewhat bulbous swelling of a whitish colour and soft consistence, and it is embraced by the true pituitary (p. 87).

Structure. The hypophysis is made up of neuroglia cells and fibres. It is invaded by epithelial cells from the pars intermedia, and colloid matter is found in it. Herring considers this to be a product of the epithelial cells, and he described its passage into the third ventricle of the brain in the cat. This is confirmed by Cushing.

Physiology.—1. **Removal.** The removal experiments of Paulesco seem to show that the hypophysis is not essential to life. If the anterior lobe is not interfered with, the animal goes on without symptoms.

2. **Action of Extracts—Hypophysin.** As in the case of the chromaffin tissue, evidence of function has been afforded by the study of the effects of administration of extracts. Oliver and Schäfer first showed that the intra-venous injection of these caused a marked rise in the blood pressure, due chiefly to constriction of the arterioles.

The active principle has not been isolated. That it is not of the same nature as adrenalin is shown by the facts that the extracts do not give the chemical reactions of adrenalin, and that in certain respects its physiological action is different. It is dialysable, it is not destroyed by heating or by reducing agents, and it is insoluble in alcohol and ether. It may be called Hypophysin, although the name Pituitrin has unfortunately also been given to it.

By perfusion experiments and by oncometric observations, it may readily be demonstrated that the extracts of the true hypophysis cause a constriction of the arterioles in mammals. In birds (ducks), on the other hand, I found that it causes a dilatation. Howell first showed that a repetition of the dose within a half to one hour is not followed by a constriction of the vessels, and Schäfer and Herring found that a dilatation and a fall of blood pressure may occur. They argued for the presence of two products of the hypophysis, and maintained that the vaso-dilator one was not cholin because the fall of pressure was not abolished by atropin. If their conclusion is correct, it would seem that the second substance, the vaso-dilator, alone acts on the arterioles of the bird. On the renal artery even of mammals hypophysin has a dilator action, and on the coronary arteries it acts as a constrictor, thus differing from adrenalin.

Hypophysin appears to act at a point peripheral to that at which adrenalin acts, since Dale has shown that it still produces its effect after a dose of ergotoxin sufficient to abolish the constriction produced by adrenalin.

On the **heart** its action is to increase the force of the contractions whether the vagus is intact or cut. After section of the vagus it does not cause the same quickening as does adrenalin. Its action on the heart appears to be upon some structures peripheral to the endings of the augmentor nerves which are stimulated by adrenalin (p. 44). This is indicated by the fact that in birds, in which I have shown that the augmentors act upon the auricles only, Watson and I found that adrenalin has no stimulating action on the ventricles, while hypophysin acts upon these structures. This action of hypophysin in augmenting the contraction of the ventricle of the bird in the absence of augmentor fibres and their terminations appears to me to be the strongest piece of evidence in favour of the direct action upon the contractile substance of muscle apart from the neuro-myal junctions.

On the **pupil** of the enucleated eye of the frog it acts like adrenalin.

On the **bladder** of the dog and cat it has a stimulating action. Not only does it act upon the muscle, but it also increases the excitability of the motor pelvic nerves to the faradic current.

On the **uterus** it also acts as a powerful excitant, causing very full contractions. At the same time it increases the excitability of the hypogastric nerves, which act as motor nerves to the organ.

Ott and Scott state that it increases the extent of contraction of the **intestine.**

Magnus and Schäfer discovered that it has a marked **diuretic action,** and Schäfer and Herring found that this occurs after a second dose, which causes no rise of the blood pressure. This diuresis is accompanied by a dilatation of the renal vessels and an increase in the volume of the kidney.

Schäfer and M'Kenzie have demonstrated that hypophysin increases the **flow of milk,** and it has been assumed that this indicates that an increased secretion is produced. But the very transitory character of the increase suggests that the action is rather upon the visceral muscular fibres of the ducts leading to an increased excretion of the milk accumulated in them, just as the flow of bile may be increased without any augmentation of secretion by a similar contraction of the muscular fibres in the bile ducts. This would explain the increased flow of milk by the well-known action of hypophysin on visceral muscle. This view is supported by the observation of M'Kenzie that atropin does not abolish the action of hypophysin, and by some unpublished observations made in this laboratory by Leonard Findlay, which show that no increase in the amount of milk yielded by a goat in the course of a day can be produced by the injection of hypophysin. Quite recently Schäfer has published a short paper giving an account of some observations on a woman, and Gavin has published experiments upon the influence of hypophysin on milk production in cows, which fully confirm Findlay's findings in the goat, and prove pretty conclusively that the production of milk is not increased.

Metabolism. The protein catabolism seems to be increased by the administration of hypophysin, according to the results of Manson and Johnson and of Falta. Crowe, Cushing and Homans also describe marked emaciation as a result of continued administration.

The results of different writers on its influence on the excretion of the inorganic constituents of the urine are so conflicting that at present no conclusion can be arrived at.

On carbohydrate metabolism its action appears to be of the same kind as that of adrenalin, but much less marked. Borchardt found that injection in rabbits causes hyper-glycæmia and glycosuria, and this observation is confirmed by Cushing and Goetsch. They further find that stimulation of the hypophysis, as in operations, is apt to be followed by glycosuria and by a decreased assimilation of sugar, so that alimentary glycosuria can be readily caused. Removal leads to increased assimilation of sugar and to a tendency to put on fat.

Thus, in cases of disease of the pituitary, the investigation of the tolerance of carbohydrates may throw light upon the question of whether the functions of the hypophysis are increased or decreased.

Falta describes a rise in the respiratory quotient after intra-muscular administration to man, indicating an increased metabolism of sugar.

The Source of Hypophysin. The evidence as regards the source of the active principle or principles of the extracts of the posterior lobe of the hypophysis is not conclusive. Herring strongly maintains that they are formed in the colloid substances of the pars intermedia, and that they pass backwards into the pars nervosa. Some observations of Swale Vincent seem to indicate that the pars nervosa is the more active part, and that, therefore, the active constituents are probably formed there.

Summary. The mode of development of the hypophysis from the nervous tissue at the base of the brain and its close connection with the true pituitary have been considered in this section. Evidence has been adduced that it is not essential to life, but that it either elaborates within itself or takes from the pars intermedia of the pituitary certain products which act upon the tissues much in the same way as adrenalin, but at a point peripheral to that acted upon by adrenalin.

II. DEVELOPED FROM THE EPITHELIUM OF THE BUCCAL CAVITY.

I. THE THYROID.

Development. The true thyroid develops as an unpaired hollow outgrowth from the fore gut ventrally to the branchial arches and in the middle line. This afterwards branches into two lateral divisions which form the two lobes of the thyroid. A trace of the original opening may persist as the ductus thyreo-glossus or foramen cæcum.

Position. Each lobe lies on the lateral aspect of the trachea below the level of the cricoid cartilage. Small accessory thyroids may exist from the lower jaw downwards to the aorta.

Structure. The organ consists of a loose fibrous tissue framework enclosing vesicles of different sizes each lined by a cubical epithelium and filled with a clear transparent mucin-like material, the colloid substance of the thyroid. This substance is strongly oxyphil and stains deeply with eosin. It appears to be formed in the epithelium, in which granules may be seen, and these are converted into colloid. This colloid may also be demonstrated in the lymph spaces between the vesicles and even in the blood-vessels.

The thyroid is enormously vascular. So abundant is the blood supply that the theory has been advanced that its function is to regulate the blood supply of the brain.

Chemistry. Kocher, from the beneficial effects of the administration of iodine in goitre, concluded that it must be a constituent of the gland.

Baumann in 1895 demonstrated its presence, and found .3 to .9 mg. per grm. of the dry substance, and 6 to 7 mg. in the whole gland of an adult man; in fact, the thyroid is ten times richer in iodine than any other organ. The element is absent in the newly-born child, and appears to be stored from the food, while the taking of iodine may increase its amount from 15 to 16 mg. The quantity present is lowest in carnivora and highest in herbivora, and it is generally proportionate to the amount of colloid in the gland. Baumann showed that it is in organic combinations. By boiling for seven hours with 10 per cent. H_2SO_4 and extracting with 90 per cent. alcohol he separated a substance which he called Iodothyrin. Oswald showed that the iodine which Baumann separated as Iodothyrin really exists in a protein combination—Iodothyreo-globulin. This is not a definite substance, but contains a varying amount of iodine. It is the active material of the thyroid, and its activity is proportionate to the amount of iodine it contains. Hence in goitre with no colloid the thyroid substance has no action. Iodothyreo-globulin is the most important constituent of the gland, forming as much as 30 to 50 per cent. of the dry substance, and in colloid goitre as much as 75 per cent.

A nucleo-protein free of iodine and without physiological action is also present.

In 1905 Reid Hunt recorded experiments to show that by feeding white mice on thyroid their resistance to the toxic action of acetonitrile is markedly raised. In one batch of mice the fatal dose in those fed upon thyroid-containing food was 1.4 mg. as against 0.32 mg. on ordinary food.

It has been suggested that this method might be used for determining the activity of various thyroid preparations, and Koch applied it to show that the greatest activity is manifested by the more complex combinations of iodine.

Physiology. On this subject an immense amount of work has been done. The speculative hypothesis of older writers may be neglected, since they were not based upon experimental investigations. J. F. Meckel about 1806 pointed out the interesting fact that enlargement of the thyroid occurs during menstruation and during pregnancy, thus showing a close relationship between the thyroid and the gonads of the female.

Another theory early put forward is that the thyroid acts as a regulator of the blood supply to the brain—a theory which has been recently revived in a modified form by von Cyon (see p. 208).

The first real advance in our knowledge of the functions of the thyroid was made through clinical medicine. In 1873 Gull described the condition now known as Myxœdema, and in 1877 Ord associated this with changes in the thyroid gland.

In 1882 Kocher described a *cachexia strumipriva* after removal of goitrous thyroids, and the Reverdins described the same condition as *myxœdème post operatoire*. Von Brunn, a few years after, described the decrease in growth and other characteristic symptoms which occur when the gland is removed in the child. Schöneman in 1892 called attention to the hypertrophy of the pituitary which accompanies the condition.

The earlier experimental work upon removal of the thyroid—such as that of Horsley in 1892—at first led to considerable confusion as to the function of the gland, because in these earlier experiments the parathyroids, first described by Sandström in 1880, were more or less completely removed with the thyroid, and symptoms of parathyroidectomy appeared.

The older experimenters had described various tremors and other nervous symptoms as due to thyroid removal, and it was noted that these were most marked in the dog and cat and were practically absent in herbivora—the reason being that in herbivora at least two parathyroids lie at a distance from the thyroid, so that a sufficient amount of parathyroid tissue is left after thyroidectomy, while in dogs and cats they are largely embedded in and are thus removed with the thyroid.

It was only when the importance of the parathyroids was recognised, and when care was taken to leave a sufficient amount of parathyroid tissue, that it became possible to study the direct effects of removal of the thyroid.

I. EFFECTS OF REMOVAL.

1. General Symptoms—A. In the Young. Hofmeister in 1892 was one of the first to describe the symptoms of thyroid removal in young rabbits, the parathyroids being left. Jeandelize has published a very elaborate account of the whole subject.

In young **rabbits** there is a checking of cartilaginous ossification, and hence the bones are only about one-third their normal length. Degenerative changes also occur in the epiphyseal line. The hypophysis cerebri enlarges. The ovaries degenerate and some follicles ripen precociously. The development of the testes is decreased.

In **lambs** the same symptoms occur. They become idiotic, and there is a decreased growth of hair.

In **goats** the bones are short and thick, but there is an increase rather than a decrease in the growth of hair. The animals also suffer from meteorism, the temperature falls, and atheroma of the aorta may occur.

In **dogs** there is decreased growth, and the bones are slender. The skull becomes globular from failure in the growth of the cartilaginous bones at the base. The belly is prominent. According to Biedl's observations, in pups there is no apathy. He states that the thymus persists. This statement is opposed to the findings of M'Lennan, and of Blumreich and Jacobi. Hypertrophy of pituitary occurs and the gonads decrease.

In **chicks** there is decreased growth, decreased development of the genitals and psychic torpor. In hens only a few thin-shelled small eggs are laid. Feeding with thyroid is said to increase the egg production (Lanz).

In the **child**, as the result of operative removal of the thyroid, there is the same decrease in growth of the bones in length but not in thickness. The periosteal ossification is not modified, but the decreased growth is at the epiphyseal line. Hence the child is stunted. There is shortening of the base of the skull, and the cranium is prominent. The gonads are undeveloped, and the secondary sex organs infantile in type. The pituitary shows enlargement. Mental deficiency is a marked symptom.

B. In Adults. The results of removal of the thyroid in the adult may be much less marked than in the young, although in certain species they are very striking.

In such animals as the dog there is wasting, apathy, loss of hair, a dry skin and advancing anæmia. In cats these symptoms are still more marked.

Kocher states that in man symptoms appear in 70 per cent. of cases of complete removal, and that, when they do not, it is because accessory thyroids are present. He considers that in operating at least one-fourth of the thyroid tissue should be left.

The symptoms of cachexia thyreopriva are generally very characteristic. Muscular weakness and mental apathy become marked; the skin becomes thickened, white and wax-like; the superficial veins stand out; a peculiar œdema develops under the skin and mucous membranes, and the pitting which occurs after pressure at once disappears. This œdema gives a look of fatness. The skin is cold and dry, and the hair becomes white and falls out.

The functions of the sexual organs are disturbed—in women menorrhagia is frequent, and in men impotence is common. If pregnancy occur, the symptoms are generally aggravated. Walter showed that after removal of thyroid tissue from newts, regeneration of amputated limbs was markedly interfered with. He concludes that this is due to an action through the nervous system, but gives no facts to prove it.

Disease. The clinical evidence of disease is fully in accord with the experimental evidence of removal.

i. **In the Young.** Setting aside endemic cretinism, to be considered presently, cases occur of *congenital* non-development of the thyroid with the symptoms just described in very extreme form. Occasionally the condition supervenes after birth—up to the fifth year—and an *infantile myxœdema* of less marked character is produced. In this there is an advancing atrophy of the thyroid gland.

Endemic cretinism is a disease of great importance on account of the number of individuals who suffer from it in the goitrous Alpine districts.

This condition is one of congenital goitrous atrophy of the thyroid, and the intensity of the symptoms varies with the profoundness of the change in the gland.

We cannot at present stop to consider the cause of this condition or the interesting experiments which have been made on animals to induce it by drinking the water of these goitrous districts.

ii. **In Adults.** Disease in the adult affords the same sort of evidence as it does in the child. The observations of Gull and of Ord have already been referred to. The disease *myxœdema* is simply a thyreoprivic cachexia.

In these cases the thyroid is small, atrophic and pale, with degenerated epithelium and increased connective tissue. Eighty per cent. of the cases are in women.

Recently cases have been described where the clinical picture is incomplete; where only some symptoms are present, and, since these improve on thyroid treatment, it has been concluded that they are milder forms of hypothyroidism.

Some maintain that *adipositas dolorosa* — or Dorcum's disease, in which local accumulations of fat, often tender to the touch, appear in various situations — is connected with hypothyroidism. Stockman, who has given much attention to the condition, is not inclined to accept this theory.

The peculiar relations of the symptoms of myxœdema to those of old age raises the question of whether the physiological involution of the thyroid plays any part in senility. Apparently it, like all other organs, undergoes an involution, but whether primary or concomitant cannot be decided.

2. Metabolism. A large number of investigators have dealt with this question.

i. Protein Metabolism. All the results recorded agree in showing that removal of the thyroid decreases the protein metabolism. In fasting it may lower it to one-third of the normal. The sparing action of carbohydrates and fats on protein catabolism is decreased, since apparently they are not so readily used.

Manseld finds that deprivation of oxygen, which usually increases the nitrogenous excretion in the urine, does not do so in animals deprived of the thyroid.

ii. **Fat Metabolism.** The metabolism of fat is said to be decreased, but the evidence upon this point is not conclusive.

iii. **Carbohydrate Metabolism.** Eppinger, Falta and Rudinger showed that after removal of the thyroid large amounts of sugar may be administered without glycosuria appearing, especially if the parathyroids are not interfered with. The sugar is stored to a greater extent and not mobilised.

It has been shown that the chromaffin system has an action in mobilising sugar, and it is thus possible that removal of the thyroid decreases the action of adrenalin in causing glycosuria. Eppinger, Falta and Rudinger state that it does act in this way, but Underhill denies the correctness of their results.

It may, however, act in another way. Evidence will be adduced later to show that the pancreas has an action in checking the mobilisation of sugar. Removal of the organ leads to a glycæmia and glycosuria, with rapid conversion of glycogen to sugar and to a formation of sugar from proteins.

Lorand showed that removal of the thyroid from a dog with pancreatic diabetes caused a decrease or disappearance of the sugar from the urine.

Eppinger, Falta and Rudinger have further investigated this point, and generally confirm Lorand's conclusions. They show that, if the thyroid has been removed a week or so before the pancreas is excised, the diabetes produced is characterised by a lessened rate of protein catabolism, and therefore a rise in the quotient Dextrose ÷ Nitrogen from 2.8 to 3.5, and a decreased loss of body weight, as compared with the condition in the dog simply depancreatised.

An increase of the colloid of the thyroid has been described after removal of the pancreas, while Falta and Bertelli found increase in the islets of Langerhans after thyroid extraction. This evidence seems to indicate that the thyroid opposes the action of the pancreas, and that it facilitates the mobilisation of sugar which is held in check by that organ.

It would thus seem that, as regards carbohydrates, the thyroid and chromaffin system act as facilitators for the mobilisation of sugar, whether from glycogen or protein; that probably the thyroid facilitates the action of the chromaffin tissue; and that both are opposed to the pancreas which keeps the process in check. It is the balance between them which regulates the carbohydrate metabolism and keeps it in the normal condition (Fig. 5, p. 185).

Eppinger, Falta and Rudinger also state that the thyroid facilitates the action of adrenalin on the peripheral blood-vessels, and that after its removal adrenalin causes a smaller rise of blood pressure. Fleming and I have not been able to confirm this in experiments upon rabbits.

2. TRANSPLANTATION.

This was first successfully carried out by Schiff in a dog in 1884. By transplanting the thyroid into the peritoneal cavity, he kept the animal alive for a long time.

Von Eiselberg proved that the grafts live. Apparently the centre of the graft generally necroses, but budding from the periphery takes place. Cristiani and also Salzer find that the activity of proliferation is more marked in animals without the thyroid, taking place in three weeks, as against six to eight weeks in those with the thyroid left.

Bucher did a successful operation of the kind on a woman after thyroidectomy, and others have also succeeded. Payr transplanted part of the thyroid of the mother in the spleen of a child of six which suffered from severe infantile myxœdema, and which had been treated, without benefit, for three years with thyroid preparations, with markedly favourable results on mind and body.

But such operations are not without danger, and the discovery in 1891 by Vessale, and by Gley, that the intra-venous injections of watery extracts of thyroid acted in the same way; and the further discovery by Murray of Newcastle that glycerin extracts given not only subcutaneously, but by the mouth, are effective has led to the abandonment of transplantation.

3. ADMINISTRATION OF EXTRACTS.

That the administration by the mouth of thyroid extracts keeps in check the symptoms of removal of the thyroid and of myxœdema of the adult, and brings about a marked improvement in infantile forms of myxœdema, is one of the best established facts of medicine. The generally lowered metabolism is restored to a normal level.

The explanation of these results is afforded in part by the study of the influence of thyroid extracts on the **metabolism** of lower animals. The effects are not produced in normal animals at once, but only after a considerable time. They are an increase in the protein and in the carbohydrate metabolism.

As regards the action upon fats, and especially upon the fats in the body of fat people, Magnus-Levy states that the increase of the CO_2 excretion and of the O_2 uptake is not sufficient to account for the disappearance of the fat. This is difficult to explain, and the question requires reinvestigation.

The continued administration of large doses of thyroid extracts produces marked symptoms of **hyperthyroidism** in man as well as in the lower animals—a rapid wasting, thirst, increased appetite, sometimes glycosuria, digestive disturbances and diarrhœa.

Kraus and Friedenthal describe in rabbits after intra-venous injection a protrusion of the eyeball, retraction of the nictitating membrane and a widening of the pupil. Hoennicke by continued administration also produced exophthalmos. In rabbits the acceleration of the heart is generally marked.

In man excessive doses of extracts may produce the same effects—psychic excitement, sleeplessness, emaciation, tachycardia and digestive troubles. Norhaft describes a case of a fat man of forty-three who in five weeks took 1000 tablets, and who developed the symptoms of Graves' disease. These symptoms disappeared when the use of the tablets was stopped.

Gudernatsch records the effects upon tadpoles of feeding with thyroid. He finds that growth stops, and that development occurs rapidly, so that the limbs grow and the tail atrophies while the tadpole is still very small.

Our knowledge of the action of thyroid extracts on the circulation is far from satisfactory. On the heart Oliver and Schäfer state that there is no action, but that a fall of arterial pressure occurs from dilatation of the arterioles.

Von Cyon and Oswald state that it increases the action of the heart when the vagi are cut. Von Cyon long ago showed that the administration of iodothyrin or iodothyreoglobulin increases the excitability of the vagus on the heart. More recently Asher and von Rodt have also found in many cases that the administration of thyroid preparations increase the excitability of the vagus and of the depressor nerve.

They also find that thyroid extracts sensitise the nerve terminations upon which adrenalin acts. Upon stimulating the splanchnic nerve the usual vaso-constriction and rise of blood pressure becomes more marked after the administration of thyroid preparations.

The study of the condition of hyper-thyroidism, produced by the continued administration of the thyroid preparation, leads to the consideration of *Graves' disease*, which seems to be due to excessive activity of the thyroid. In it the various symptoms produced by hyper-thyroidism are manifest.

The thyroid shows parenchymatous hypertrophy, with marked vascularity and proliferation of the epithelium of the vesicles. In later cases increase of the connective tissue is found. Curiously enough, the percentage of iodine is decreased. Does this mean a lessened power of fixing and storing the iodothyreoglobulin?

Hypertrophy of the thymus is common—but Graves' disease is apt to occur in people of the thymo-lymphatic type. Gierke holds that in these cases operative interference leads to bad results. Possibly there is an antagonism between thyroid and thymus.

The heart's action is exaggerated and quickened, and the left ventricle becomes hypertrophied. There is increased vaso-motor activity, and flushings are common. The temperature is also frequently increased. Exophthalmos from widening of the eye-slits and protrusion of the eyeball from contraction of the muscle of Müller are present.

As shown by Magnus-Levy, there is a most marked increase in the rate of chemical exchange and in the total oxidation of the tissues. The power of assimilating sugar is decreased, and it tends to appear in the urine.

The work of Asher and von Rodt support the view that in Graves' disease there is an increase of thyroid secretion in the blood. In order to get rid of any adrenalin that might be present, they treated the blood with formaldehyde, which destroys adrenalin, and found that the injection of the serum in a series of cases caused increased vagus excitability, increased action of adrenalin, and increased irritability of the splanchnic and of the depressor nerves.

The treatment which has proved most successful is ligature of some of the vessels of the thyroid or removal of part of the organ. Kocher states that 76 per cent. of the cases so treated were cured, and 14 per cent. were benefited. The mortality is between 3 and 4.7 per cent. The utility of X-rays has not been demonstrated as a means of decreasing the function of the thyroid.

General Conclusions. The evidence is thus quite conclusive that the thyroid exercises a marked action on the development and growth of soma and gonads. That its action on the soma is a direct one, and not through any action on the gonads, is indicated by the marked difference in the changes in the characters of bone development after thyroidectomy and after castration. In the former there is a failure in the bone formation at the epiphyseal junction, in the latter a too prolonged continuance of growth at this point. In the former the growth of periosteal bone is not interfered with, in the latter it is decreased, and the bones are more slender.

Is its action on the gonads direct or through the soma? The action is so marked and so out of proportion to the nutritional changes in the soma that there can be little doubt that it is a direct one, and that we are justified in concluding that the thyroid is of importance in the growth of the gonads in the pre-pubertal period of life.

Influence of Nerves upon the Thyroid. The work of Asher and von Rodt seems to indicate that the activity of the production of its internal secretion by the thyroid is under the control of the nervous system. Taking the sensitising action on the abdominal sympathetic nerves as their index of an increase of the secretion into the blood, they tried the effect of stimulating the nerves of the thyroid, and found that it increased the effect of stimulating the splanchnics. From this they concluded that the nerves to the thyroid had caused an increased production of the active substance.

Summary. After describing the development, structure and chemistry of the thyroid, its physiology has been considered in the light of experimental and of clinical evidence. The results of removal, of suppression of function by disease or by arrested development, and the effects of excessive action brought about by administration of the active principle of the gland and by Graves' disease have been dealt with. The conclusion has been arrived at that the thyroid supplies to the organism an internal secretion which has a stimulating action on the course of metabolism, thus increasing the activity of development and of growth of soma and gonads. Its manifest action on the activity of the central nervous system has been pointed out, and its probable action upon the termination of the true sympathetic and the para-sympathetic has been discussed.

II. THE PITUITARY.

Development. The true pituitary—the anterior part of the so-called pituitary body or hypophysis cerebri—develops like the thyroid from an epithelial out-growth of the anterior part of the alimentary canal.

This outgrowth is upon the dorsal aspect of the canal. It is, according to some, entirely derived from the ectoderm of the oral cavity, but others maintain that the endoderm of the fore-gut is also implicated in its formation.

Growing upwards it forms a series of branches, and becomes a gland-like structure with solid columns of cells and no acini. It embraces the anterior part of the true hypophysis cerebri, and is convex anteriorly and concave posteriorly. It has a pale yellow or greyish-red colour and hard consistence, while the true hypophysis has a white colour and is soft. Accessory glandules may remain along the track of the developing pituitary.

Structure. It consists of two somewhat different parts :

1st. A pars anterior consisting of dense columns of cells of two kinds—(1) The chief cells or chromophobe cells with a protoplasm which does not stain readily. They are large and ill defined. (2) The chromophil cells, which may be divided into (*a*) those staining readily with eosin, and having a finely granular protoplasm, and (*b*) those staining with basic stains—larger cells with coarser granules. It is very vascular, the capillaries being sinusoid. The nervous supply is from the sympathetic.

2nd. A pars intermedia, a layer composed of several rows of cells, and separated from the anterior lobe by a cleft. It is closely applied to the posterior or nervous lobe—the true hypophysis (p. 64). Colloid matter is present between some of the cells, and these are not of the two distinctly separated classes found in the anterior part. This part is not so vascular.

Physiology. By Galen the pituitary was considered a structure, the function of which is to separate the mucus from the brain for secretion. Since his time, many other theories resting on bases even less substantial have been put forward. They do not require consideration.

The first real advance was made through clinical observation. Marie in 1886 described a peculiar overgrowth of the bones which he called acromegaly, and in 1891, in conjunction with Marinesco, he showed that this is usually associated with tumours of the pituitary.

Experimental work on the subject has proceeded on certain definite lines.

1. **Removal.** The operative difficulties of reaching the pituitary and of removing one part alone proved a great obstacle in the way of older experimenters. They generally attempted to reach the structure through the roof of the mouth and base of the skull. It was only when Paulesco in 1907 devised the method of opening the cranial cavity in the temporal region and raising the brain, so as to expose the side of the hypophysis and pituitary, that satisfactory results were obtained.

Operating in this way and on different animals, Paulesco, Cushing Crowe and Homans and Biedl have shown that removal of the true pituitary—as distinguished from the hypophysis—is rapidly fatal, death generally occurring within a few days or weeks, and being preceded by muscular tremors, slow pulse and respiration and an ante-mortem fall of temperature.

Removal of the posterior part, the true hypophysis, as already stated, is not fatal.

Partial removal of the true pituitary in young animals is not generally fatal, and is followed by decreased growth and persistence of infantile characters, hypertrophy of the thyroid, atrophy of the gonads and an accumulation of fat chiefly in the omentum and retroperitoneal tissues.

According to Paulesco, section of the stem of the pituitary produces all the symptoms of removal, but Cushing is unable to confirm this.

These results are confirmed by recent experiments of Aschner, who removed the whole of the pituitary body from young dogs less than three months old by the oral method. Some of the animals lived for more than six months. In both males and females the genital organs remained small. Spermatogenesis was delayed, and was sparse and atypical. The uterus remained small, and in the ovaries the interstitial cells almost disappeared. The development of ova was delayed for six months, and the ovaries remained less developed than in the normal animals. A marked deposition of fat appeared, and the hairy coat and bones remained infantile.

Benedict and Homans have recorded a series of observations on the metabolism of dogs from which the pituitary was either completely or nearly completely removed. These lived for a considerable time.

They found that the gain of body weight was retarded, that the skin was thickened and the hair tended to fall out, that there was a gain of fat and that the gonads did not develop. The temperature fell, and the heat-regulating mechanism was interfered with. The rate of the heart decreased, and concomitantly the rate of respirations diminished. The excretion of carbon dioxide was markedly decreased.

2. Transplantation. Cushing, by transplanting the anterior lobe, has succeeded in prolonging the life of the animal, the graft apparently continuing to live for at least a month.

3. Administration. Cushing states that by injecting extracts he succeeded in keeping animals alive after removal of the pituitary, and in improving the condition of patients suffering from hypo-pituitarism.

Schäfer, in the Croonian Lecture, 1909, gives experiments to show that feeding and also grafting pituitary increases the growth of young animals. His results, however, are not very definite, and they are not confirmed by the findings of Goetsch and Cushing, while the observations of Aldrich give no support to the view that the rate of growth is modified by the addition to the food of the pituitary, of the testicle or of the ovary.

4. Physiological Hypertrophy of the Pituitary. During pregnancy the pituitary hypertrophies, and the hypertrophy is due chiefly to an increase in the chief or chromophobe cells. It has been maintained that pre-existing pregnancy may actually be determined by the development of these cells, although after each pregnancy and during lactation they undergo a process of involution. This condition of the pituitary may, perhaps, be associated with the thickening of the subcutaneous tissue of the nose, lips and hands which so frequently accompany pregnancy.

Hypertrophy of the pituitary is also caused by castration and by removal of the thyroid. This, of course, indicates a reciprocal action of these structures on one another.

The thyroid and pituitary have more or less a common origin, and their action upon metabolism, growth and development is in some respects similar. They appear to be compensatory to one another.

On the gonads the pituitary has an augmenting action. Both structures have an important influence on growth and development. When the gonads are removed, the pituitary undergoes what is probably a compensatory hypertrophy. But without the pituitary, complete development of the gonads appears impossible.

5. **Disease.** The consideration of these hypertrophies of the pituitary leads to the study of the condition described by Marie as *acromegaly*. This disease generally affects adults. It begins with fatigue, muscular pain, apathy and sleepiness. In the later stages the sexual activity is decreased, and in women, menstruation generally stops.

A diffuse increase of the soft parts of the face and increased growth of the bones of the face occur. The superciliary ridges become more prominent, the nose enlarges, the lower jaw increases, the lips thicken and the tongue hypertrophies.

Later, the hands and feet increase, partly by increase of the connective tissue generally and of the true skin, partly by growth of the terminal phalanges. Very often symptoms of intra-cranial tumour are present. Glycosuria is evident in a large proportion of cases, and is probably due to implication of the posterior lobe—the hypophysis (p. 69). As regards the metabolic changes, nothing very definite is known. A retention of phosphorus, calcium and chlorine has been described, but the evidence is by no means satisfactory.

The progress of the disease is usually slow. After death the most constant change found is in the pituitary, which shows either a hypertrophic hyperplasia or tumour formation.

Cases of treatment of the disease by operative removal of the pituitary have been recorded by Hochenegg, by Cushing and by Exner. In some of these cases a marked improvement occurred, and the deformity caused by the hypertrophy of the soft parts and the bones was decreased. In two of the cases menstruation reappeared, and in these two hypertrophy of the thyroid was observed.

The evidence thus seems to indicate that the symptoms of the disease are due, in part at least, to exaggerated and possibly perverted action of the pituitary. Tumour formation can hardly be expected to give rise to a pure stimulating action such as might be produced by electrical stimulation. Cushing's careful analysis of his series of cases seems to prove that the disease begins by exaggerated functional activity of the pituitary, characterised by increased growth of bone and, in some cases, by precocious sexual development; but that later a condition of decreased activity supervenes, with decrease of sexual activity.

The true hypophysis is also involved, and hence the assimilation of glucose is altered either positively or negatively.

Marie's investigations on acromegaly suggested that cases of giantism may be related to increased action of the pituitary. A study of living examples of this condition and of the skeletons of some of the famous giants has tended to confirm this view. Many of these giants during life have shown a persistence of the infantile habit—they were often mentally deficient and apathetic, the growth of hair was often poor and the reproductive organs were undeveloped. Post-mortem, the sella turcica, in which the pituitary rests, has been found enlarged. It would almost seem as if giantism was an acromegaly of youth, while true acromegaly was a manifestation of the disease occurring after the epiphyseal cartilage had ossified.

A condition which, in the light of the physiological observations of Cushing on the effects of the partial removal of the pituitary in young animals, seems to be associated with a decreased activity of the pituitary in young people, has been described by Fröhlich. It has been called *dystrophia adiposo-*

genitalis. It is characterised by deposits of fat often on the buttocks and breast, and by the non-development of the sexual organs. Cases have been described with lesions of the pituitary. Von Eiselberg described one in which the removal of a tumour growth was followed by amelioration of the symptoms.

The evidence thus points to the pituitary acting somewhat in the same way as the thyroid upon development, growth and metabolism.

Evidence has been adduced in the case of the thyroid that its action upon metabolism is through the nervous system, probably through the terminal plexuses of the true sympathetic and of the para-sympathetic systems. But in the case of the pituitary there is not the same evidence.

Summary. The development of the true pituitary, as an epithelial upgrowth from the buccal cavity, and its subsequent association with the hypophysis, its division into a pars anterior and pars intermedia, and the structure of each of these has been described. The effects of removal, of transplantation, of administration of its substance after removal, and the pathological changes which occur in acromegaly, have been dealt with. The two stages of this disease, the first irritative, the second atrophic, and their effects on metabolism, have been indicated.

The conclusion is arrived at that the pituitary, like the thyroid, produces an internal secretion which stimulates the metabolism and growth of tissues, and more especially of the gonads and of the connective tissues, including bone.

So far no indication is forthcoming as to whether the internal secretion acts directly on the tissue elements or operates through the nervous system.

III. DEVELOPED FROM THE MID-GUT.

I. THE PANCREAS.

Development. The pancreas is developed as a paired outgrowth from the mid-gut. Each division branches and again branches to form a compound racemose gland. From the epithelium lining the ducts, separate groups of cells grow out to form solid islands of epithelial tissue—the islets of Langerhans. These are very richly supplied with blood-vessels.

It is, I think, probable that two kinds of islets exist, the true islets formed as described above and false islets which may be produced by changes in the acinal tissue, as was first described by Dale.

That true islets exist is shown by embryological research, by the observation of Rennie that in teleostean fishes the islets are definitely encapsulated, by the distinctive staining reaction with Bensley's neutral gentian described by Kirkbride, and by the recent work of Homans.

Physiology. Primarily the pancreas is to be regarded as a digestive gland, which pours its secretion into the duodenum, there to play a most important part in the digestion of food.

But just as Bernard discovered that the liver, which is also primarily a digestive gland, has most important relations with the general metabolism, so von Mering and Minkowski have demonstrated that the pancreas also is intimately related with the metabolic processes throughout the body. And the pancreas, like the liver, is chiefly concerned with the metabolism of carbohydrates.

In 1889 these investigators discovered that removal of the pancreas in dogs leads to a condition of true diabetes. Sugar appears in the urine and increases in the blood, there is polyuria, great thirst, rapid wasting, with increased appetite and increased excretion of nitrogen. The animal rarely survives for more than four weeks.

This discovery has been confirmed in many species of animals in all groups of vertebrates by a number of investigators.

The removal of the pancreas must be complete. If one-third or even one-fifth is left, the symptoms do not develop.

The question arises whether it is the islets or the acinal tissue, or both, which are the important element in this result. The evidence cannot be considered as conclusive, but so far as it goes it points to the islets. Cases have been recorded where a part of the pancreas has been ligatured off from the rest, and where, on examination, it has been found to consist entirely in islet tissue. M'Callum in 1909 (quoted by Kirkbride) described such a case in a dog where removal of the sound piece of pancreas led to only a slight glycosuria, but where subsequent removal of the degenerated part composed, as afterwards found, entirely of islet tissue produced a very marked glycosuria.

Minkowski showed that transplanting a piece of the pancreas prevented the onset of symptoms, and he thus proved that the effect of removal is through an internal secretion and not through the nervous system, as was maintained by Pflüger.

Subsequent removal of the graft induced the condition of diabetes.

So far the administration of pancreatic extracts has failed to prevent the onset of symptoms or to check them when developed. Hedon gives some not very satisfactory evidence that the blood coming from the pancreas has some influence. He states that, when a cross circulation is arranged between two dogs, one normal and one rendered diabetic by removal of the pancreas, so that the blood of the diabetic dog flows through the tail of the pancreas of the normal animal *into the portal system* of the former, the glycosuria is markedly decreased. When the blood enters the systemic vein, the effect is not produced. He further says that he finds that injection of the blood of the pancreatic vein into the mesenteric vein of a diabetic dog decreases the glycosuria. At first sight these observations would seem to point to a direct action of pancreatic secretion on the liver, but the facts that the mere establishment of a cross circulation may reduce glycosuria and that the glycæmia is not reduced in these experiments materially decrease their significance.

The direct action of the pancreatic secretion upon the liver indicated by these results is in accord with the old observation that glycosuria does not occur in frogs if the liver as well as the pancreas is removed.

As to **how the internal secretion acts,** various theories have been advanced. Lépine thought that it stimulated the combustion of sugar in the tissues. This view seemed to be supported by the finding of Cohnheim that sugar is not oxidised by muscle juice alone outside the body, but that it disappears in a mixture of muscle juice and pancreatic extract. This finding, however, was not confirmed by the careful investigations of Claus and Embden. Certain results obtained by Knowlton and Starling, to be presently considered, give, however, some support to the theory.

The view that the pancreas controls the mobilisation of sugar both from the glycogen stored in liver and muscle and from the protein molecule seems most in accordance with the evidence we at present possess.

In the first place, the rapid disappearance of hepatic glycogen and the marked decrease of muscle glycogen on removal of the pancreas supports this view. In fasting or in protein feeding, the persistence of sugar in the urine and the increased excretion of nitrogen show that there is a loss of control over the formation of sugar from proteins. This too rapid mobilisation of sugar leads to its increase in the blood and its excretion in the urine. Hence it is less available as a source of energy, and fats and proteins have to be utilised. As a result, the various abnormalities of metabolism which follow the withdrawal of carbohydrates manifest themselves. Cathcart and Taylor have shown that creatin appears in the urine, and the modified metabolism of fats leads to the appearance of β-oxybutyric acid and to the various symptoms of acidosis.

That the combustion of available sugar by the tissues is interfered with, is indicated by the low respiratory quotient on a carbohydrate diet. Normally on a carbohydrate diet the oxygen consumed is equal to the carbon dioxide excreted: $\frac{CO_2}{O} = 1$. But on a protein or fatty diet, since the proportion of oxygen in the molecule is so small, the oxygen consumed exceeds the CO_2 excreted, and the respiratory quotient falls to less than 1. Hence a low respiratory quotient on a carbohydrate diet indicates the non-utilisation of sugar.

That there is a real failure of certain tissues to use sugar is indicated by the recent experiments of Knowlton and Starling, confirmed by Maclean and Smedley. They perfused the excised heart of the normal and of the depancreatised dog with blood containing sugar, and they found a much greater utilisation of sugar in the heart of the normal than in that of the depancreatised and diabétic animal. Knowlton and Starling record experiments to show that the addition of pancreatic extracts to the blood circulating through the heart restores the power of the muscles to use sugar. The results of Maclean and Smedley do not so definitely confirm this observation.

It would thus seem that the pancreas exercises a double influence on carbohydrate metabolism, first checking its mobilisation in the liver, and, secondly, determining or facilitating its utilisation in the tissues.

Does the pancreas act directly upon the liver cells and other carbohydrate storing structures, or does it act indirectly through the nervous system?

In favour of the latter view is the antagonism of adrenalin and the pancreatic secretion—the former mobilising sugar, the latter checking its mobilisation. Since we have seen reason to conclude that the former acts by activating or stimulating the endings of the true sympathetic in the liver, it may be argued that the endocrinous secretion of the pancreas inhibits them.

Loewi has described an increased action of adrenalin on the pupil in cases of diabetes, presumably of pancreatic origin, and argues from this that the pancreas must have a checking influence on all the true sympathetic terminations. The problem lends itself to further investigation on lower animals, extending them to the heart, blood-vessels, uterus and intestine.

Summary. The pancreas is primarily a digestive gland, from the epithelium of the developing ducts of which specialised masses of cells, the true islets of Langerhans, are formed. Secondary islets may possibly be produced later from alteration in the secreting acini. Removal of the pancreas has been found to cause a condition of diabetes, the onset of which may be checked by grafting pancreatic tissue. In this condition there is a too rapid mobilisation of sugar, and a failure on the part of muscular tissue to use sugar. These results indicate that the pancreas produces an internal secretion or secretions which hold in check the mobilisation of sugar, thus opposing the secretions of the chromaffin tissue, of the hypophysis and of the thyroid, and which facilitate the utilisation of sugar by the muscles as a source of energy. The former effect is probably brought about by an action upon the terminations of the true sympathetic system in the liver. About the essential nature of the latter action, nothing is known.

II. THE MUCOUS MEMBRANE OF THE SMALL INTESTINE.

The fact was discovered by Bayliss and Starling that from the mucous membrane of the upper part of the small intestine an extract can be made which, when injected into the jugular vein, causes a copious flow of pancreatic juice. The active constituent of this extract they called **Secretin.** Although the substance has not been isolated, it is known to resist the action of heat and of acids, to be diffusible, and not to give any of the protein reactions. They also confirmed the observations of Wertheimer and Popielski that the introduction of acid into the duodenum caused a secretion of pancreatic juice, even after the vagi and splanchnic nerves have been cut and the spinal cord destroyed. They further state that, when all the nerves to a loop of intestine have been cut, the introduction of acid causes a flow of pancreatic juice. From this they conclude that the action of the acid is not of the nature of a peripheral reflex, as suggested by Wertheimer and by Popielski, but that it is due to the production of secretin from a hypothetical prosecretin, and that this, passing into the circulation, reaches the pancreas and acts directly upon it. Not only is the secretion of pancreatic juice increased, but the flow of bile is also augmented.

About the facts recorded there can be no doubt. But whether this chemical stimulation of the pancreas is the normal mechanism in evoking secretion is not so clear. At first sight everything seems simple. Acid chyme enters the duodenum from the stomach. Pancreatic juice is required for its further digestion. The acid of the chyme changes prosecretin into secretin, which at once acts upon the pancreas to call forth its activity.

Were the pancreas, as is the liver, supplied by blood coming from the intestine, the evolution of such a mechanism would be easily understood. But in order to reach the pancreas the secretin must be carried through the portal circulation of the liver, through the right heart, through the lungs and into the systemic arterial system, and so at length reach the pancreas just as it reaches every other organ of the body.

It may, of course, be urged that all internal secretions are primarily poured into the blood of the veins, and have to pass through the lesser circulation to reach the structures upon which they act. But in no other case is the action of the internal secretion so definitely from one organ to a particular and closely adjacent one, in no other case is it so difficult to understand how such a lengthy route should have been evolved.

On the other hand, the work of Pawlow has quite clearly shown that pancreatic secretion is evoked by stimulation of the vagus—that in fact there is a direct nervous control. And, I think, it is perhaps somewhat rash to allow ourselves to be carried away by the brilliant experiments and fascinating explanations of Bayliss and Starling. It may very possibly be that, in the future, the nervous control will be shown to have a greater importance than we at present believe it to possess.

Edkins has described the formation of an internal secretion similar in character to secretin which is produced from the mucosa of the stomach and which seems to act in supplementing the nervous mechanism of gastric secretion.

IV. DEVELOPED FROM THE BRANCHIAL CLEFTS.

I. THE THYMUS.

Development. The thymus, as already stated, is derived from epithelial outgrowths from the branchial arches, and in Petromyzon it seems to persist

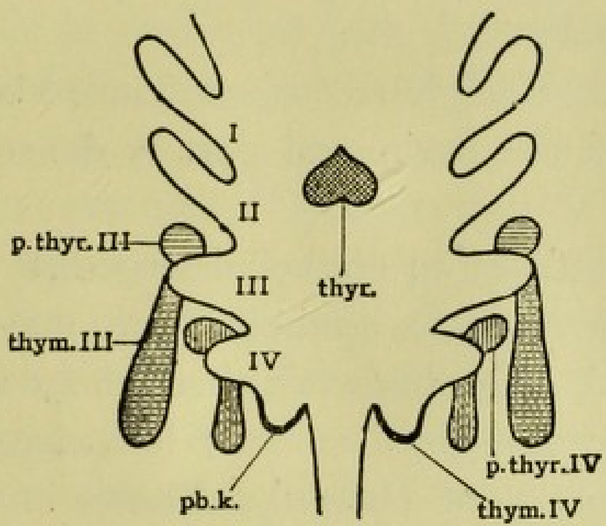


FIG. 3.—To show the origins of the thyroid, thymus and parathyroids.
From Ergebnisse der Physiologie

in this condition. The close association of such a structure with the original direct channel of the blood-flow to the body suggests the occurrence of some modification in the blood *en route* for the tissues.

In mammals the thymus is derived chiefly from the ventral end of the third branchial cleft, but a small bud from the fourth cleft forms a little nodule of thymus lying in the thyroid (Fig. 3).

Position. In most mammals it is situated chiefly in the upper mediastinum of the thorax, lying just in front of the cephalic end of the heart and the great vessels. In the guinea-pig it is entirely confined to the neck, and lies on each side of the trachea, extending from the larynx downwards. In birds it lies as a series of separate masses down each side of the neck.

In mammals it consists of two chief lobes, one on each side, each lobe being subdivided into a number of small lobules.

Structure. Each lobule is surrounded by a fibrous capsule, and the peripheral part is denser than the central.

It is essentially an epithelial structure and, while the organ persists, its epithelial cells may be traced as a network or groundwork throughout the lobules and as a series of large more or less circular bodies —the corpuscles of Hassall. These, in their fully developed state, must be considered as degenerative products of the epithelium. In the embryo they appear as masses of reticulum cells. They are invaded by polymorpho-nuclear leucocytes, and the protoplasm of the cells shows the development of granules staining deeply with basic stains.

The epithelial groundwork has its interstices filled with lymphocyte-like cells. The nature of these is still under dispute. Hammar maintains that they are true lymphocytes derived from outside the epithelial thymus, Stöhr contends that they are formed from the epithelial cells and that they are really epithelial in nature.

The evidence upon the subject is very fairly stated by Hammar. He points out that the evidence in favour of their epithelial or autochthonous origin is:

1st. The presence of intermediate forms. He is inclined to maintain that the existence of these has not been proved.

2nd. The special character of the mitosis of thymus cells as compared with that of lymphocytes. He is sceptical of the possibility of demonstrating this.

3rd. The absence of lymphocytes in the rest of the body while these small cells are seen in the thymus. He cites Bryce's work on the development of lymphocytes in Lepidosiren which shows that they are formed outside of the thymus. This evidence does not seem to be of much importance either way as regards the origin of the cells *in* the thymus.

4th. The absence of lymphocyte infiltration round the thymus which should be present if migration were taking place. This seems of little importance.

5th. The change of the lymphocyte-like cells to epithelial cells. This is simply a repetition of the first argument.

6th. The chemical difference between the thymus and lymphatic glands. Ivar Bang gives the following analysis :

	Thymus.	Lymph Gland.
Protein - -	15.52	13.79
Nucleinate -	3.15	0.69
Ash - - -	1.59	1.05

In favour of the immigration theory he cites :

1. The morphological similarity of the small cells of the thymus and the lymphocytes—a somewhat difficult point to determine in dealing with cells so small as these.

2. The physiological similarity as shown by the presence of amœboid movement and the similar reaction to X-rays.

3. The evidence of immigration from surrounding tissues.

4. The partial disappearance of these cells in fasting, and their restoration by immigration after feeding. That the restoration is by immigration seems to me a difficult point to establish.

5. The observation of Ritchie that injecting the thymus of guinea-pigs into ducks yielded a cytolytic serum acting not only on the cells of the thymus but also upon the lymphocytes of lymph glands. Since the thymus emulsion injected contained blood, the possibility of a double cytotoxine has to be considered.

The recent work of Hart certainly strongly supports Hammar's view as to the lymphocyte nature of the small cells.

If this is the case, it brings the structure of the thymus into accord with that of the tonsil, a derivative of a higher branchial cleft, where epithelial outgrowths become surrounded by true lymphoid tissue.

Reviewing the evidence we possess, we are, I think, forced to confess that further work must be done before any definite conclusion can be arrived at.

Pensa and others have described peculiar long cross-striped cells like muscle fibre in many vertebrates, which Hammar has called *myoid* cells. Herman considers that these are modified epithelial cells. Pensa finds that they are distinct from the epithelial network.

In Amphibia especially, spaces of different kinds are found in the thymus.

1. Vacuoles in the epithelial cells. 2. Lacunæ between the cells. 3. Enclosed vesicles with colloid or mucous material.

Some of these are lined by epithelial cells like the rest of the thymus groundwork, and some of the lining cells have cilia upon their free margin.

In triton and rana esculenta, Pensa finds rows of epithelial-like cells along blood-vessels, and in the adder several rows of cells projecting into the vessels. They are not endothelial, and he considers them of special significance in the production of an internal secretion.

Life-history of the Thymus. Beginning as an epithelial structure, the thymus early shows the appearance of the small cells, the nature of which has been already considered. Parts of the epithelial groundwork increase, and form accumulations of cells. These undergo degeneration, and produce the Hassall's corpuscles. In most animals the organ reaches its greatest size in relationship to the body weight about the time of birth, but further work is wanted upon this point. After birth the rate of growth generally decreases, although in the dog at least, according to Klose and Vogt, this is not the case for some days. Growth goes on till about the onset of sexual maturity, when a true involution of the organ occurs, and it decreases in bulk. Fibrous tissues and fat cells extend into the lobules as the true tissue atrophies, and finally it is reduced to a mass of adipose tissue with some islands of thymus remaining.

An estimation of the relative size of the thymus to the body weight in some animals is given below:

WEIGHT OF THYMUS TO WEIGHT OF BODY.

Man.		Dog.	
Birth	1 to 240	Birth	1 to 250
5 years	1 " 690	8 to 14 days	1 " 170
10 years	1 " 960	2 to 3 months	1 " 1200 to 1600
15 years	1 " 1140		
20 years	1 " 2356		

Rabbit.		Guinea-pig.	
7 weeks	1 to 423	Under 2 weeks	1 to 420
¼ year	1 " 923	½ to 1 month	1 " 1000
½ year	1 " 1250	1 to 2 months	1 " 1700
1 year	1 " 1517	2 to 3 months	1 " 2400
2 years	1 " 1922		

In birds it is said that the thymus does not undergo involution (Soli), but from my own observations in ducks I am inclined to think that this statement requires reinvestigation.

Not only does this true physiological involution occur, but, at any period in the early life-history of the thymus, accidental temporary involution is apt to be produced by any interference with the nutrition of the animal. Thus in the rabbit a fast of three days may reduce the thymus to one-half. This reduction appears to be due to the disappearance of the small cells, chiefly from the peripheral part of the lobules.

Physiology.—Removal. The life-history of the thymus points to its being a structure of importance during the period of growth and development, and, in order to get the most marked results from its removal, this should be done at the period of its greatest relative size, and in animals in which it is best developed after birth.

A difficulty which has met the experimenter is the position of the thymus in the thorax in the majority of mammals. This makes the operation a serious one, since the danger of injury to the pleura and of pneumo-thorax and of injury to the great blood-vessels have to be faced. In addition to these dangers is that of sepsis, the onset of which probably markedly interfered with the results of some of the older experimenters.

On the other hand, the position of the thymus high up in the neck of the guinea-pig renders its removal a very simple operation, and for this reason I have used these animals in my investigations. But the state of maturity in which the guinea-pig is born, and the fact that even under two weeks the weight of the thymus is only 1 to 420 of the body weight, while in the dog of the same age it is 1 to 170, is a possible indication that even at birth in the guinea-pig the organ is not playing so active a part as it does in some other animals.

On account of the difficulties and dangers of operation, the results of the older experimenters may be neglected.

Restelli in 1848, using sheep, dogs and calves, had a very high mortality. In the dogs which survived he noted an increased and perverted appetite.

Friedleben's work (1850) has long been considered a classic. For his removal experiments he used dogs and kids. Only a few survived. One dog lived for four months, and ate voraciously, consuming corks and other similar objects. Before it died it emaciated. In the kids he observed that, if any of the thymus was left, regeneration tended to occur. He also records imperfect bone development.

The work of Abelous and Billard on frogs, afterwards refuted by Hammar, and the experiments of Tarulli and Le Manaco and of Ghika, threw no fresh light on the problem.

In 1904 Goodall and I undertook a series of observations on young guinea-pigs, and we then concluded that removal of the thymus has no influence on the rate of growth of the animal, but that it is followed by a slight decrease in the number of leucocytes in the blood, which lasts for about two months. The increase of leucocytes, which occurs in the normal guinea-pig during pregnancy, after injection with tubercle, and after injection of terebene occurs also in thymusless animals. But there seemed to be a less marked leucocytic response to injection of staphylococci and streptococci, and a decreased resistance to these infections.

Simultaneous removal of thymus and spleen was not fatal in the guinea-pig.

M'Lennan describes a method of removing the thymus in the rabbit and kitten, and records the results of his experiments. He came to the conclusion that the growth is more active after removal of the thymus, and that the epiphyseal cartilages grow more rapidly. He says that, after removal of the thymus, the thyroid was only to be found with difficulty, and that the organ was more cellular, had larger adenoid masses, and that the glandular spaces were smaller. He further states that thyroidectomy causes a disappearance of the thymus, and quotes Blumenreich and Jacobi as getting similar results. Unfortunately he gives no details of his various experiments, and his results as regards the relations of the thyroid and the thymus have not been confirmed by subsequent investigations.

Basch published an important series of papers between 1903 and 1908. He removed the thymus from dogs of from three to four weeks old—rather older than the age at which, according to Klose and Vogt, the thymus is largest. He found that the bones became softer and tended to bend, that fractures tended to heal badly and with less callus. He gives the following analysis:

EARTHY SALTS OF DRIED BONE.

Normal animal - - -	65 per cent.
Thymusless animal - -	32.02 per cent.
" " - -	34.24 per cent.

He also states that there was an increased excretion of calcium. The animals became sluggish, there was a loss of intelligence, and their weight was less than that of the controls. Cramps of the muscles, tonic and clonic, tended to develop, and there was increased electrical excitability, especially in the opening cathodal response.

Klose and Vogt have also done a large series of experiments upon pups. They selected the tenth day after birth for operation, as at that age the thymus has attained its maximum development. They operated on 54 pups in ten sets, each with a control, and they were able to follow the changes in 25.

They do not give the individual protocols, but they describe generally the changes as divided into three stages.

1st. A Latent Period of about fourteen days, during which symptoms are practically absent, but which gradually passes into—

2nd. An Adipose Period, which lasts for two or three months. The animal develops an enormous appetite, becomes fat and sluggish and is easily tired. Its gait becomes more and more infantile, and it becomes stupid. It gradually passes into the third stage—

3rd. A Cachectic Period, during which, although it continues to eat enormously, its weight falls and it emaciates. Muscular tremors, differing from those of parathyroid tetany, develop: it becomes imbecile: the hair becomes rough and falls out, and the animal finally dies.

They confirm Basch's observation of the softening of the bones, which have also been confirmed by several other investigators.

They found in these animals a simple hyperplasia of the pancreas, and of the ovaries and testes. They state that removal of the spleen after thyroidectomy causes a rapid advance of the symptoms, and they therefore consider that the spleen has a compensatory action. In this they confirm the old observation of Friedleben.

The most unsatisfactory feature of the work of Klose and Vogt is the absence of proper protocols of the individual experiments. They make no real attempt to explain the symptoms, although they put forward the hypothesis that an acidosis is produced, which leads to increased solution and excretion of lime salts. The question of calcium distribution and excretion they did not study.

The most curious part of their results is the onset of symptoms at a period when the thymus is no longer actively growing, but is reduced from 1 to 170 to 1 to 1200 of the body weight. This suggests that removal of the thymus must upset the metabolic balance, so that those organs which take on the action of the thymus as it disappears fail to exercise their proper effect.

The most recent study of the effects of removal of the thymus is by H. Matti.

He concludes that Klose and Vogt are wrong as to the early cessation of growth of the thymus in pups, and maintains that involution does not begin till after the fourth month. His operations were therefore done between the eighteenth day and the eighth week. In the first few thymus glands removed, parathyroids were examined for but were not detected, and in the other experiments the presence of the usual four parathyroids was determined after death. He finds that after a varying latent period, during which the animals showed a less gain of weight than the controls, increased slowness of movements and muscular weakness were observed. The bones became softer. These symptoms increased and death supervened.

The bone changes resembled those of rickets. Fractures were apt to occur. The long bones were shorter, thicker and more easily bent. The epiphyseal cartilages were markedly thickened and irregular. The cortical parts of the diaphyses were thicker, with a thin compact layer and much spongy bone in the marrow cavity. There was in fact a development of bone poor in lime. The muscular fibres showed degenerative changes.

There was evidence of a hypertrophy of the cortex supra-renalis and the thyroid was slightly increased.

In general the follicles of the spleen appeared to be hypertrophied, and simultaneous removal of thymus and spleen in one case was at once fatal. The pancreas was increased. Changes in the hypophysis were not marked, but in the spinal cord and brain, the changes described by Klose and Vogt were observed.

In a few cases these changes did not appear, and the author concludes that probably functionating parts of thymus IV. were present, or that a vicarious action of other endocrinous structures had masked the symptoms. Seiler examined the blood, and the changes described by him were not very pronounced.

Transplantation of the thymus was successfully tried by Basch to prevent the onset of symptoms after removal of the thymus. He found that grafts in the abdominal cavity survived, but that those placed under the skin were absorbed and had no effect. More recent work on the subject has yielded no results of importance.

The injection of **extracts** of thymus into the blood stream was found by Svehla to cause a marked fall of blood pressure. But since a similar fall occurs with many other tissue extracts it is of little significance.

Feeding with thymus in thymusless animals was tried by Klose and Vogt in their dogs, but it produced diarrhœa and an aggravation of the symptoms.

Recently Gudernatsch has described experiments of feeding tadpoles upon thyroid and upon thymus, and he finds that the former arrests growth and produces rapid development, while the latter has the opposite effect and causes the tadpoles to grow to a great size without undergoing metamorphosis. These observations seem worthy of repetition and extension.

Relation to the Gonads. The thymus has a very definite relation to the gonads. It has been for long known to butchers that the thymus of bullocks is larger than that of bulls. Henderson, at my suggestion, made a careful investigation of this question. He finds that the thymus of castrated cattle is nearly double the size of that in uncastrated and that its atrophy is delayed.

I have confirmed these results in guinea-pigs.

But the converse also holds. I found that in young thymusless guinea-pigs, before the period of sexual maturity, the growth of the testes was usually more rapid than in normal animals. After the onset of sexual maturity at 300 gr. weight no difference was observed.

	Thymusless.		Normal.	
	Average body weight.	Average weight of testes.	Average body weight.	Average weight of testes.
Under 200 gm. -	165	0.23	152	0.18
,, 300 gm. -	256	0.88	252	0.60
Over 300 gm. - -	330	1.24	322	1.33

An increase in the size of testes and ovaries is also recorded by Klose and Vogt in dogs, although in their table they seem to have confused the weights of ovaries and testes.

At first I was inclined to regard these results as indicating that the thymus and testes had a reciprocal inhibitory action on one another. But it seemed possible that the same changes would result from removal of thymus or testes if each was compensatory to the other, if each exercised an influence on growth and development, and if, when one was removed, the compensatory increase in the activity of the other led to hypertrophy. To test this, thymus and testes were removed in a series of young guinea-pigs, and it was found that, while removal of one or other caused no delay in the rate of growth, removal of both sets of organs simultaneously caused a marked delay in the growth.

In the female I have been unable to detect any reciprocal relationship between thymus and ovaries.

It may, therefore, be concluded that the thymus like the gonads, in the male at least, exercises an influence on the rate of growth. Possibly at a very early age, before the testes have attained their full influence on the metabolism, this is more dominant; and it may persist longer in some animals than in others. Hence possibly the more marked symptoms recorded in the dog than in the guinea-pig after removal of the thymus.

Mors Thymica. Sudden deaths in apparently healthy children and adults occur, sometimes when under an anæsthetic, without any manifest cause of death being discovered upon post-mortem examination. In some of them an abnormally large thymus is found. These cases led to the theory that the enlarged thymus was the cause of death—that there is a *mors thymica.* At first it was supposed that the action of the thymus is a mechanical one, and that the enlarged gland produces its effect by pressing on the trachea, or on the heart, or on the great nerve trunks of the neck. The last explanation was supported by reference to the old observation that a spasm of the larynx and a condition of asthma is sometimes associated with a voluminous thymus. Matti considers the evidence as regards the possible mechanical action of the thymus in compressing surrounding organs, and comes to the conclusion that pressure of an enlarged thymus, especially on the vessels, may be a factor in causing death.

Another theory has been put forward, that the condition may be caused by an abnormally large production of the internal secretion of the thymus.

But no evidence is forthcoming, and until we know far more than we do at present about the action of the products of the thymus, we are not warranted in accepting such a pure speculation.

In fact, the evidence does not point at all clearly to the thymus as being the cause of these deaths. Many cases of sudden death occur without enlargement of the thymus having been observed.

But there is some evidence that a certain number of individuals show a peculiar anomaly in development, characterised by an excessive growth of the lymph tissue throughout the body and of the cortex of the thymus, with, at the same time, other anomalies of growth and metabolism. In these people subcutaneous fat is generally excessive; the reproductive organs are small and remain infantile in type; the hair, and especially the pubic hair, does not grow. The older physicians described this condition as the lymphatic temperament, and recognised that the vitality is low.

Wiesel tried to divide such individuals into a true thymus class with hypertrophy of the thymus—more especially of its reticulum—and no marked change in the lymph tissue elsewhere, and a true lymphatic class in a number of which the thymus is not affected.

It would rather seem that such individuals show a condition of imperfect development, in which the various ductless glands participate. There may be in fact an insufficiency of several endocrinous structures. Whether on account of this or on account of the general imperfect development, they are more easily killed than others, and hence they are more liable to sudden death from comparatively small disturbances. The condition of their thymus gland has probably nothing to do with the fatal issue, and the term thymus death may be considered a misnomer.

Summary. We have thus seen that the thymus is formed as epithelial outgrowths from the third and fourth branchial arches; that these outgrowths form a branching network, at some places concentrated into masses of cells which degenerate and form the corpuscles of Hassall; that the network becomes filled up with lymphocyte-like cells which are either true lymphocytes migrated from without or which are formed from the epithelial cells. In every animal the thymus reaches its greatest weight, relative to the weight of the body, either at the time of birth or shortly after this, and about the age of puberty it ceases to grow and begins to atrophy. "Accidental" atrophy may also occur in malnutrition. Removal of the thymus from young dogs, in which animals it attains its greatest weight in relationship to the body weight, leads to a definite train of symptoms—imperfect growth and defective calcification of bone, deposit of fat with subsequent wasting, instability of the central nervous system—with tremors or convulsions, and increase in the electrical reactions of the nerves, followed by advancing decrease of functional activity of the upper neurons. Death finally supervenes. The condition is accompanied by compensatory hypertrophic changes in the testes. The conclusion is drawn that the thymus produces an internal secretion which exercises a marked influence upon development and growth, but that its removal may be in part compensated for by the internal secretion of the testes in the male. The secretion also acts upon the central nervous system, increasing the stability of the reflex arcs (Fig. 6). Evidence is wanting as to whether its action on metabolism is directly upon the tissues or through the peripheral nervous mechanism. The condition known as *mors thymica* has been discussed, and reasons for considering the term a misnomer have been given.

II. THE PARATHYROIDS.

These structures, small yellowish bodies lying in close relationship to the thyroid, were first described by Sandstroem in 1888.

Origin and Development. Like the thymus, they are formed from epithelial outgrowths from the third and fourth branchial clefts, but from the dorso-cranial aspect instead of from the ventral (Fig. 3). Another small cystic outgrowth from the side of the fourth cleft forms the post-branchial body.

The outgrowth from the third cleft, parathyroid III. or the lower parathyroid, lies free of the thyroid in all animals and in man at the aboral pole. That rom the fourth cleft, parathyroid IV., in many animals comes to lie inside the thyroid, but in man it lies on the upper dorsal surface, and it may be called the upper parathyroid.

As already mentioned, Pepere describes a development of parathyroid tissue inside of the thymus—specially well marked in the rabbit. According to Harvier and Morel it is also present in the cat. Accessory parathyroids may be present at different parts of the neck.

Structure. Each consists of a fibrous tissue framework with columns of cells occupying the spaces. These cells are of two kinds: (1) Chief cells, polygonal in shape with a protoplasm not readily stained and with nuclei staining deeply; (2) Oxyphil cells, smaller than the last and with a granular protoplasm staining with eosin. In some places towards the margin there may be masses of colloid surrounded by oxyphil cells. It is the increase in this colloid which in certain conditions gives the parathyroids the appearance of thyroid tissue.

Position. In such carnivores as the dog and cat parathyroid III. lies outside the thyroid at its upper end, while parathyroid IV. is embedded in the organ or lies closely upon it.

In the sheep and goat, parathyroid III. is at a considerable distance from and above or in front of the thyroid, while parathyroid IV. is embedded in it.

In the rabbit, parathyroid III. lies below the thyroid (about 1 cm.), while parathyroid IV. is inside it. In birds the parathyroid lies behind, aborally, to the thyroid.

The positions and relationship of the parathyroids to the thyroid are important, because these structures may be removed to a greater or less extent when the thyroid is excised. Hence symptoms due to parathyroid removal were at one time ascribed to removal of the thyroid.

Physiology.—Removal. Sir Astley Cooper in 1824 experimented with dogs, and found that removal of the thyroid was fatal. He of course also removed at least two, probably all, the parathyroids. Schiff in 1856 got a similar result. Weiss in 1880 was the first to describe the onset of muscular spasms after thyroidectomy and to recognise the resemblance of the symptoms to **tetany.**

After the introduction by Billroth of the operation of thyroidectomy for goitre, J. and A. Reverdin and Kocher in 1882-83 independently described symptoms of tetany in some cases after thyroid removal.

Gley in 1890 showed that generally in herbivora these nervous symptoms do not occur unless the parathyroids, lying some way from the thyroid, are removed along with it.

Apparently ignorant of Gley's work, and failing to recognise the significance of Sandstroem's observations, Horsley in 1891 described as one of the effects of removal of the thyroid in monkeys a peculiar muscular tremor.

In 1896 Vassale and Generali were able to show that removal of the parathyroids in dogs induced tetany, while removal of the thyroid alone produced a peculiar cachexia. This has been confirmed by many subsequent observers.

The symptoms produced vary with the amount of parathyroid tissue which is removed. The acute form may be seen in dogs and cats, when both thyroid and parathyroids are excised. There is generally a latent period of twenty-four to seventy-two hours during which marked thirst and loss of appetite may manifest themselves. This is followed by fibrillar twitching of individual muscles of the face, head, back and tail. After twenty-four hours these become more severe and more frequent. In the cat a stretching out of one leg and a shaking of the foot as if to remove water is often seen. The gait is stiff, with tonic cramps, and a peculiar clubbed position of the foot. Clonic spasms appear and become more frequent. The animal rapidly wastes and dies within ten days.

In rabbits the symptoms are well marked, and are sometimes produced in a modified form even by removing the two external parathyroids, while in some old rabbits all the parathyroids along with the thyroid may be removed without symptoms appearing. But in these cases, Haberfeld and Schilder found that subsequent removal of the thymus produced the symptoms—probably because of the removal of the embedded parathyroid tissue.

Generally speaking, removal of more than two parathyroids leads to symptoms of tetany, which may be acute or chronic.

Gozzi describes a series of partial and of complete removals of the parathyroids in dogs. Total removal produced death within five days, but when supplementary parathyroid nodules existed, life was prolonged for from nine to twenty-three days. Total thyro-parathyroidectomy he found to be less rapidly fatal than complete removal of the parathyroids alone. After total removal of the thyroid, leaving the external parathyroids, the animals lived for months.

Sometimes after two or three parathyroids have been removed, a condition of **latent tetany** is developed. The animal is free of symptoms, and these may not become manifest till pregnancy or lactation supervenes. Pepere emphasises the point that the symptoms are more severe in pregnancy.

Iselin states that the young of rats, on which parathyroidectomy had been performed, showed increased muscular excitability to the electric current, and suffered very acutely from parathyroidectomy—dying within a few hours of the operation.

As regards the part of the neuro-muscular mechanism involved in the tetany following parathyroid removal, the evidence points to the spinal cord as the part chiefly affected, since section of the nerves abolishes the seizures in the muscles supplied. Biedl finds that after section of the cord in the dorsal region, the muscles of the hind limbs undergo sudden contractions, with intervening relaxations, while those connected with the upper part of the cord and brain show a more tonic condition—probably due to an influence of the labyrinths and cerebellum.

Horsley and Lanz state that, after removal of the cortex cerebri, the condition continues on the contralateral side.

Mustead finds that the tetany is not modified by removal of the cortex cerebri, or by section of the dorsal roots of the spinal nerves, and he concludes that the primary motor neurons are the structures implicated. He also finds that it does not occur below the point of section of the spinal cord, and considers that this indicates that some part of the encephalon below the cortex cerebri is also involved.

A certain number of animals show *no symptoms* of tetany after what appears to be complete thyroparathyroidectomy. In all probability such cases are to be accounted for by the fact that outlying pieces of parathyroid tissue have been frequently observed even as far down as the aortic arch, while, as already stated, Harvier and Morel have shown that nodules may occur in the thymus of the cat, and Pepere finds that a considerable amount may be present in the thymus of the rabbit. These variations in the symptoms may also be due to the fact that removal of the parathyroid reduces the stability of the central nervous system, but that some other disturbing factor, *e.g.* pregnancy, is required to upset it sufficiently to cause the manifestation of the symptoms.

Thompson, Leighton and Schwartz show that ligature, so as to produce a slow interference with the blood supply, may lead to no tetanic symptoms, but that a slow wasting occurs and that the animal dies in a cachectic condition.

In the human subject, as already stated, tetany has been produced as the result of the removal of parathyroid with the thyroid in the treatment of goitre, and now special precautions are taken to avoid this. Even with these precautions, there is a certain risk that injury to the blood supply of the parathyroids may lead to temporary tetany or to a tetany which may remain latent and may manifest itself if pregnancy supervenes.

The evidence that the disease of children known as *tetany* and characterised by the hyper-excitability of the neuro-muscular mechanism, and by more or less marked attacks of cramps of groups of muscles, is due to injury or decreased functional activity of the parathyroids is not definitely proved. Some cases have been reported with hæmorrhages into the parathyroids (Erdheim), but in others no changes were detected. It must be remembered, however, that functional inadequacy is not necessarily accompanied by manifest structural change, and the fact that parathyroid treatment has relieved a number of cases of tetany indicates the probable association of the condition with morbid conditions of these structures.

Metabolism. In the ordinary acute tetany, after parathyroid removal, symptoms of disturbed metabolism have little time to manifest themselves. But in more chronic cases, such as may be produced by gradually ligaturing off the parathyroids, it is found that the animal emaciates, and that the hair becomes rough and falls out. In rats Erdheim has described a peculiar change in the teeth—a want of calcification of the dentine and enamel which leads to fracture.

The fact that **calcium salts** have a depressing influence on the excitability of the neuro-muscular mechanism led to the hypothesis that possibly parathyroidectomy might produce its effect by decreasing the calcium content of the neuro-muscular mechanism.

The experiments of MacCallum and Vögtlin, 1908-9, upon dogs seemed to show that removal of the parathyroids caused a decrease in the amount of calcium in the blood, and in the brain. As to the excretion of calcium they say that "on the whole the general impression is . . . that the excretion of calcium salts is increased." They also describe a very great increase in the ammonia content of the blood. Musset and Goodman failed to confirm MacCallum's findings, and von Reuss and Welde got exactly opposite results.

Jean V. Cooke gives analyses to show that the brains of dogs dying of tetany contain a slightly *greater* proportion of calcium than do those of normal dogs. The excretion of magnesium in the urine she finds to be increased, but not the excretion of calcium. Her results are thus opposed to those of MacCallum and Vögtlin.

Leopold and von Reuss investigated the calcium content of the tissues of normal and of parathyroidectomised rats. In the adult they found no marked difference, but in young animals a decrease. Further, they found that the bones were richer in calcium and the soft parts poorer. They suggest that mere alteration in the combination of calcium may explain the symptoms of tetany. This view receives some support from the influence of injections of citrates in producing muscular spasms, probably from the combination of the calcium ions in a non-ionised condition. One observation which I have made upon a cat with parathyroid tetany, shows that the symptoms are markedly increased by the subcutaneous injection of sodium citrate. By removing the calcium from its ionised condition, its influence in controlling the activity of the nerve centres may have been decreased.

It is probable that the administration of calcium simply acts as a sedative. Berkeley and Beebe find that magnesium and strontium act in the same way. Further, the fact that bleeding, which must still further deplete the body of calcium, decreases the symptoms seems to be opposed to the view that a diminished calcium content is a factor in determining the onset of tetany. The administration of calcium produces only a temporary amelioration of the symptoms, but its repeated administration is capable of keeping them in check.

The **protein metabolism**, as indicated by the excretion of nitrogen in the urine, after removal of the parathyroids has been studied by several investigators.

Musser and Goodman describe a rise in the excretion of total nitrogen—an increased protein catabolism—and an increase in the proportion of nitrogen in the form of ammonia. Morel got a similar result.

More recently J. V. Cooke has confirmed these results. She further finds that the other nitrogenous constituents of the urine are unaltered. In two cases lactic acid was present in the urine at the time of the attacks of tetany.

It is well known that the administration of ammonia produces muscular tremors and convulsions. But the amount required to do this is large. Massen and Pawlow found that about 2 mg. per hundred c.cm. of blood was necessary to cause twitching.

Albertoni failed to find any increase in the ammonia content of the blood after parathyroidectomy. And, while MacCallum and Vögtlin describe an increase, Carlson and Jacobson record no change, a finding which is confirmed by Greenwald.

There is thus little evidence of the occurrence of an acidosis, and the appearance of lactic acid in the urine is probably the result of increased muscular action.

Direct evidence is thus wanting that disturbances in metabolism are the primary and causal element in the onset of tetany, and it may well be that the withdrawal of the product of the parathyroids establishes the condition of instability in the central neurons which is the basis of the tetany, and may also be the basis of the metabolic disturbances.

The only evidence against this view is the temporary benefit derived from bleeding and transfusing animals in tetany. But the indication this seems to afford of the presence of some poison in the blood is rather negatived by the failure to produce tetany by the injection of the blood of animals suffering from the condition.

There is some evidence that the parathyroids have an influence on the metabolism of carbohydrates. Partial removal seems to lower the tolerance for sugar so that when given by the mouth or hypodermically it tends to appear in the urine. This may possibly mean that the parathyroids act like the pancreas in checking the mobilisation of sugar in the liver, possibly by increasing the storage as glycogen. Further investigations upon this subject are required.

While the vast majority of investigators have found a definite group of symptoms after parathyroidectomy, certain observers have failed to get these results.

Blum got negative results, but his observations were probably not sufficiently carefully carried out.

Swale Vincent and Jolly record a large series of experiments on various species of animals. Some of their results are tabulated below :

	Number of observations.	Death.	Grave symptoms.	No grave symptoms.
Cats -	15	10	3	2
Dogs -	5	—	4	—
Foxes -	4	4	—	—
Monkeys -	7	—	2	5

They go back to the old theory of Blumenreich that the parathyroids are merely potential parts of the thyroid. They base this conclusion partly on the morphological similarity of thyroid and parathyroid tissue, on the fact that removal of thyroid according to them leads to hypertrophy of the parathyroid and a change to thyroid-like tissue, and on the results of their experiments. Their experiments seem to me to support the work of other investigators who maintain that the parathyroids have an independent action. A very full statement of their views is given in Swale Vincent's *Ductless Glands*.

Transplantation of the Parathyroids. This subject is very fully dealt with by Thompson, Leighton and Schwartz. They point out that Eiselberg in 1892 transplanted the thyroid gland after thyroidectomy and found that no symptoms occurred, but that, when the graft was removed, tetany occurred. The internal parathyroids were, of course, transplanted along with the thyroid. The same result has been obtained by others.

Of those who have attempted to transplant the parathyroid, many have failed to get any result. Others have found that the graft very soon atrophies, although the symptoms of tetany may for the time be controlled. Biedl, Pfeiffer, Mayer, Halsted, as well as Thompson, Leighton and Schwartz, have succeeded in getting the graft to grow in some cases, and have found that when it was removed symptoms of tetany supervened. Halsted found that the grafts only grew after removal of parathyroids, and that the persistence of very small fragments of .5 × .25 mm. is sufficient to keep a dog alive.

Kocher records a case in which thyroid alone was transplanted into the medullary cavity of a bone prepared in a special manner and where no symptoms supervened till the bone was removed.

Thompson, Leighton and Schwartz found that merely trephining the bone checked the onset of tetany, but did not delay the development of cachexia and death. How this acts they cannot explain. The observations should certainly be repeated.

Eiselberg records the case of a woman who suffered from chronic tetany in whom transplantation was followed by amelioration of the symptoms.

Administration of Extracts of Parathyroids. MacCallum and Davidson report a case of tetany, after parathyroidectomy in a dog, in which the symptoms were repeatedly relieved by intra-venous injection of an emulsion of parathyroids of as many as twenty to thirty dogs. The symptoms recurred and were again suppressed by the same treatment.

Other observers have got no result on feeding with parathyroid.

Beebe isolated the nucleo-protein of the parathyroids and found that it is the constituent which is active in suppressing symptoms of tetany. Its activity is destroyed by heating. Halsted has used the preparation with success in a case of post-operative tetany after two operations on a large colloid goitre, and Pool had a similar result.

Some experimenters have found that the administration of thyroid preparations control the symptoms. Biedl argues that since the thyroid contains about 350 parts of thyroid to one of parathyroid, this result cannot be due to the presence of parathyroid substance in the preparation. But, since Halsted has shown that so tiny a bit of parathyroid tissue is sufficient to suppress symptoms, this argument loses some of its force. Berkeley and Beebe do not confirm this observation on the beneficial effects of thyroid preparations. Ott and Carlson and Jacobson find the condition benefited by the injection of extracts of the hypophysis.

Ott has described other actions of parathyroid extracts. In cats he states that they cause increased contractions in the isolated intestine and uterus, a fall of arterial pressure, a marked polyuria—in some cases a tenfold increase in the urine secreted in half an hour—and the appearance of glucose in the urine. These observations require to be repeated.

Lundborg (1904) suggested that alteration in the activity of the function of the parathyroids may have a causal relation to various modifications of the neuro-muscular mechanism. Assuming that the parathyroids exercise a checking influence on the activity of the mechanism, he considers that tetany, the laryngismus stridulus that is so often associated with it, myoclonus, paralysis agitans and myotonia may be due to decreased functional activity, while the various forms of myasthenia may be related to an increased activity.

Influence of Nerves on the Parathyroids. The question of how far the activity of the parathyroids is controlled by the nervous system has not been fully investigated. Asher, and subsequently Edmunds, have ligatured the superior and inferior laryngeal branches of the vagus of one side, and subsequently removed the opposite lobe of the thyroid with the parathyroids, thus leaving two parathyroids the nerves to which were cut. Symptoms of tetany appeared. Such results seem to indicate that the parathyroids are under the control of the central nervous system.

Summary. The parathyroids, like the thymus, have been found to develop from the epithelium of the third and fourth branchial clefts. Two definite parathyroids are thus found on each side, but accessory parathyroids may also be produced and may exist in the thymus. The close association of the parathyroids with the thyroid, and the existence of these accessory parathyroids, has rendered it somewhat difficult to study the effects of removal. Parathyroidectomy is followed by a definite train of symptoms, of which the most prominent is a condition of instability of the spinal reflex arcs with the occurrence of peculiar spasmodic movements—the condition of tetany—and with an advancing cachexia, which may be present even when the symptoms of tetany are in abeyance. It is possible to remove these symptoms by grafts, while the tetany may be checked temporarily by the administration of calcium or of strontium salts, which depress the excitability of the spinal centres. The influence of parathyroidectomy on the metabolism has been discussed, and the conclusion is arrived at that the parathyroids yield an internal secretion which, probably by acting directly upon the spinal centres, or possibly by in some way controlling the metabolism, maintains a checking influence upon the reflexes. The question of whether the metabolic disturbances are primary to the nervous disturbances or mere accompaniments of these is still undecided.

V. DEVELOPED FROM THE MESOTHELIUM OF THE GENITAL RIDGES.

I. THE GONADS.

The gonads, or sex glands, undoubtedly exercise a marked influence on the metabolism, development and structure of the body, and most materially modify its activities. It is of interest that they were the first structures experimentally proved to have such effects. Berthold of Göttingen in 1849 removed the testes of cockerels and transplanted them into other parts of their bodies, and found that the sex characters persisted. He concluded that the testes yield a product which acts on the other organs of the body.

The gametes or reproductive cells are massed in the gonads. It is unnecessary here to discuss their primary origin; but the fact that, in such simple forms of animal life as Ascaris, the precursor of the gametic cells can be definitely shown to be separated from the progenitor of the soma cells at the first mitotic division, renders it highly probable that in all more complex forms there is a more or less similar early separation of the two elements, and that the gametes thus live as parasites upon the soma, or, to put it in another way, that the soma develops to support and nourish the gametes, and thus to secure the continuance of the life of the species. Possibly the two might be described as commensals.

In vertebrates the first manifest differentiation of the gametes from the soma cells occurs on the genital ridge, where certain of the cells lining the cœlom become the progenitors of the gametes.

Development. The gonads develop in the genital ridge of the embryo by ingrowths of mesothelial cells.

In the **male** the testis is formed (*a*) By the arrangement of these cells in tubules. In these tubules are the true gametic cells—the spermatogonia, from which the spermatozoa are formed—and the supporting cell of Sertoli. Recent evidence clearly shows that these have the same origin as the gametic cells. (*b*) By the intercalation of other cells between the tubules as the interstitial cells of Leydig. Their origin from the mesothelium has not been quite definitely proved. In character they are certainly epithelial. They are large cells containing lipoids. Some observations by Dr. Gemmill on males, made in the course of an investigation on the development of the ovaries in Amphibia, seem to show the mesothelial origin of these cells.

In the **female** the mesothelial cells, which have grown inwards, become arranged in rounded bodies, the Graafian follicles, with the gametic cell, the ovum, in the centre, and the supporting, nourishing or ancillary cells of the zona granulosa round about it. Between the follicles are interstitial cells resembling those of the testes.

The origin of these interstitial cells has been much debated, and even at the present day it is considered by many as not yet determined.

The investigations of Louise M'Ilroy, carried out in this laboratory, leave little doubt, I think, that they, like the follicle cells, are mesothelial cells of the genital ridge, and that they are modified gametic cells.

She describes the primitive germ cells as first differentiating into "capsular cells," the germ epithelium, which is protective in function, and "oogonia." These latter form (1) oöcytes, (2) capsule cells of the follicles, and (3) interstitial cells or reserve cells.

The commensal relationship of soma and gametes raises two questions—

1st. Do the gametes, or the gonads in which they lie, modify the metabolism of the soma?

2nd. Does the metabolism of the soma react upon the gametic cells?

I. Influence of the Gonads on Development and Growth.—(A) In the Male.

1. Removal. From a very remote time the effect of castration of young male animals and of boys has been well known.

The most manifest result is upon what may be called the secondary sex organs and characters, while the whole soma also undergoes changes in metabolism and development.

In mammals the most marked change is in the prostate and seminal vesicles, which cease to develop, and if developed undergo atrophy. The penis does not undergo so marked an arrest of growth, and if developed does not show distinct atrophy.

As regards the general body characters, the various organs grow, but tend to have an infantile character. In man the supra-ciliary ridges are undeveloped, and the pelvis and larynx are in form like those of the child. The latter condition leads in man to the highpitched childish voice of the eunuch. Union of epiphysis and diaphysis is delayed, and the bones tend to be long and slender. The hair development is scanty, especially on the face. There is a tendency to the development of fat often on the buttocks and on the breasts. The temperament is generally phlegmatic. Occasionally fat does not develop, and the individual may be more active.

In lower mammals the results are much the same as in man. The bones do not grow so markedly in girth, the epiphyseal cartilages persist and the bones are long and slender. The secondary sexual characters do not develop. Stags, when castrated young, do not develop antlers. If castrated at the time when antlers should grow, these form a clump or "peruke," and tend to persist instead of being shed annually. If the stag is castrated when the horns are on, these fall off, and next season clumpy, or "peruke," antlers grow. In the prong buck, which has hollow deciduous horns standing straight up, castration leads to the growth of horns bending downwards and inwards near the eyes. The horn sheath is not shed and becomes composite. In the sheep, castration leads to absence of growth of horns and to the development of the appearance of the female rather than of the male. In the eland, in which both sexes have horns, castration does not stop the growth of the horns in the male.

Generally speaking, after castration the animal is less active and tends to fatten readily.

In birds, castration of young cocks leads to non-development of the male type of plumage, of the wattles, and of the characteristic male type of voice.

In invertebrates the influence of the testes on the soma is sometimes well marked, as is shown by the effects of the destruction of the testes in the spider crab by a parasite, *Sacculina.* The crab tends to develop female characters, *e.g.* it grows egg-bearing abdominal appendages.

In the adult male, removal of the gonads has naturally not the same marked and manifest influence on the morphology of the soma. But upon the general metabolism the influence is distinct although less marked.

2. Precocious Development of Gonads—Pubertas Præcox. The influence of the sexual organs on the soma is well seen in cases of pubertas præcox. A very instructive case is recorded by Sacchi of a boy who had been perfectly normal till five and a half years of age, and who, between that age and nine and a half, showed enormous growth of bones and great muscular development. His voice became deep, and he had a growth of hair on the pubis and on the face. At nine and a half he had a long black beard. The left testicle showed a tumour growth. This was removed, and proved to be an alveolar carcinoma. After this all the symptoms of sexual precocity disappeared.

In these cases the epiphyses tend to join the diaphysis early, and hence the long bones, and the whole individual, tend to be shorter. The periosteal growth of bone is very vigorous.

Cases of pubertas præcox have been associated with tumours and other growths of the cortex of the supra-renal bodies, but these will be considered when dealing with the functions of that structure. It is sufficient to point out just now that the cells of the cortex supra-renalis are developed from cells very similar to those yielding the gametes and interstitial cells on the genital ridge (p. 171).

Other cases have been described to which tumours of the pituitary body seem to stand in causal relationship to the condition.

3. Transplantation. The early observations of Berthold of Göttingen upon the effect of transplantation of the testes in arresting the disappearance of male characters in young cocks have been already referred to.

Nussbaum, in 1904, showed that in castrated frogs which, at the breeding time, showed no growth of the grasping thumb-pad on the fore feet and no hypertrophy of the muscles of the fore limbs, the implantation of testicular tissue in the dorsal lymph sac caused the development of these sex characters. These results are fully confirmed by those of Steinach on rats and guinea-pigs. These will be considered later more in detail.

4. Administration of Extracts. Various investigators have found that the injection of extracts of the testes produces the effects of precocious sexual development, that the union of epiphysis and diaphysis of the long bones is hastened and the bones are thus shortened.

Loewi states that feeding young capons with testicular substance causes the development of the secondary sexual characters.

Meisenheimer maintains that in castrated male frogs the injection of ovarian extract acts in a similar manner to the injection of testicular extract, causing a distinct if somewhat modified growth of the thumb pads. He holds that the action is not specific, but that the products of both organs are the same, and act to increase the metabolism and to facilitate the development of the somal characters which should normally appear.

Brown-Séquard, in 1889, recorded results of administration of extract of testes to himself. He describes an increase in physical strength and mental activity. These conclusions have not been borne out by the work of subsequent investigators.

5. **Involution.** In most animals, and very markedly in the human subject, with advancing age sexual activity wanes, and the gonads undergo a partial atrophy. Curiously enough, this is frequently accompanied by a hypertrophy of the prostate.

The general vigour and activity of the body diminishes, the skin tends to wrinkle from the decrease of subcutaneous fat, and the hair may fall out.

These changes of the soma may, of course, be mere concomitants of the sexual changes, but since the changes produced by castration are somewhat of the same character, the evidence appears to support the view that the changes in the gonads are primary and at least partly the cause of the somal changes.

The evidence thus seems conclusive that in the male the gonad, by producing an internal secretion, exercises a direct and specific influence upon the whole soma, increasing the activity of growth, moulding the whole course of development, and so modifying the metabolism of nerve and muscle that the whole character of the animal is altered.

Meisenheimer contends against the view that the gonads have this direct and specific action on the development of the soma, and recounts a series of experiments upon lepidoptera, in which the sex organ was removed in the caterpillar stage, and the imago emerged without ovaries or testes, but with the secondary sex organs developed, and with the sex reflexes developed.

In the face of the mass of evidence clearly pointing to a specific action of the gonads, Meisenheimer's contention that this action is not specific, but is simply one of general stimulation, cannot be sustained. The products of the gonads of both male and female probably have a stimulating action on the metabolism, but such an action seems totally insufficient to explain the strikingly specific effects of the products of the two different gonads.

What is the **nature of the action?** That it is not through any nervous reflex mechanism is shown by the effects of transplantation and of injection of testicular extracts. It is manifestly through some internal secretion.

Is this secretion yielded by the testes as a whole or by some special part of the organ?

That it is not the gametic cells which determine the development of sex characters has been shown by the experiments of Shattock and Seligmann on sheep and birds.

They found that ligature of the vas deferens in young animals leads to atrophy and disappearance of the spermatogenic cells, but does not interfere with the cells of Leydig or of Sertoli, and that it does not interfere with the development of the sexual characters.

Bouin and Ancel have brought forward evidence to show that it is the interstitial cells which are essential. They removed one testis in the rabbit and ligatured the vas deferens of the other testis. They found, first the condition described above, but later, after ten to twelve months, a degeneration of the cells of Sertoli and a marked hyperplasia of the interstitial cells.

They found that some rabbits, after ligature of the vas deferens, developed characters which accompany castration, and they believed that this occurred when nerves as well as the duct were ligatured.

Vincent and Coleman found that ligature of the whole spermatic canal with the blood-vessels acts in the same way as castration.

The influence of X-rays in destroying the spermatogenic cells, but leaving the cells of Sertoli and the cells of Leydig intact, was demonstrated by Tandler and Gross in 1898. They experimented on the roebuck, and showed that such secondary sexual characters as the horns persist.

The evidence thus seems satisfactory that the interstitial cells of the testes produce an internal secretion which profoundly influences the whole development and growth of the body and the habits of the animal. One may use the term suggested by Heape—*Gonadin*—for their internal secretion, recognising that it is different in the male and in the female.

How far the development of this gonadin is modified and controlled by other structures in the body, such as the thyroid, thymus, inter-renals and pituitary, we shall have to consider in dealing with the inter-relations of the various glands. There is good evidence that each acts upon and is in turn acted upon by the gonads.

The evidence is thus conclusive that the interstitial cells act upon the soma. Do they likewise act upon the gametes? Upon this further work is necessary.

Hofmeister, in 1872, noted these cells in the human embryo at four months' gestation, and says that they constitute two-thirds of the whole testes. At eight years of age they constitute only one-tenth of the organ, but at puberty they again increase.

In some animals at certain seasons they are very well developed, and have very much the character of the cells of the cortex supra-renalis, containing fat droplets and yellowish pigment.

A careful study of the condition of these cells throughout the œstrous cycle of the male mole is recorded by Tandler and Gross. They find that during the breeding season the interstitial cells are displaced by the enlarged tubules, but that after œstrus, as the tubules become reduced, the interstitial cells again increase, and reach their maximum just before the onset of the next œstrus period.

The evil effects of precocious sexual activity in many animals would suggest that in some way the excessive development of the gametic cells is associated with a withdrawal of the influence of the interstitial cells from the soma to the gametes.

It would seem from such considerations that the interstitial cells are the connecting link between the soma and gonads through which they are enabled to react on one another, and through which their several activities are co-ordinated. Their mode of development with the gametes, their undoubted relationship to the growth and development of the soma, and the cyclic change they undergo throughout the œstrous cycle, all point to this conclusion. Through their action, the relationship of the gametes to the soma becomes symbiotic rather than parasitic.

(B) In the Female. The evidence may be dealt with under the same divisions which were adopted in considering the male.

1. **Removal.** The evidence afforded by castration in the female is much less abundant than in the male, since the operation is rarely performed before puberty in women, and is not so frequently performed in female as it is in male domestic animals, either mammals or birds. In fowls it is attempted in the making of poulets, but it is never complete. The oviduct is cut so that the eggs are simply shed into the abdomen and absorbed.

My own observations on guinea-pigs, undertaken to study the influence of castration on the growth of the thymus, show a non-development of the uterus, but no apparent change in the growth of the body.

Marshall and Carmichael and Louise M'Ilroy also record the same change in various mammals.

Removal or disease of the ovary is apt to be accompanied by somatic changes in the direction of the acquisition of the characters of the opposite sex. Thus, cases have been recorded where hinds have developed horns, and the ovaries have been found diseased.

In birds, too, atrophy of the ovaries is apt to be followed by the assumption of male plumage. This has been recorded in several species, among others in the duck and pheasant.

It would thus appear that the females, in many species at least, have latent male characters which are suppressed by the ovaries.

In certain crabs the invasion of the young gonad by parasites of the Bophyridæ group destroy these structures. There is then a suppression of the secondary sexual characters.

The negative results of Meisenheimer in butterflies have been already referred to (p. 146).

2. Pubertas Præcox.. There is not the same evidence that pubertas præcox in the female leads to general changes in the soma so marked as those found in the male. That it is accompanied by development of the mammary gland and by growth of pubic hair is well known. Lucas, quoted by Guthrie, records the case of a girl of seven years of age who had menstruated several times, and who had well developed mammæ and pubic hair. A tumour of the ovary resembling a round-celled sarcoma was removed. Menstruation ceased and the secondary sex characters gradually disappeared.

Whether the condition has the same influence on the epiphyseal union of the long bones, and hence upon the height of the individual as it has in the male, has not been investigated, although gynæcologists express the opinion that in cases of sexual precocity the individuals are usually short. It is of some interest to find that the observations of Westhof (Marburg) on the age of the first occurrence of menstruation puts it about six months later in tall women than in short.

	Brunette.	Fair.
Tall - - - -	17.5	17.7
Medium - - -	17.3	17.4
Short - - - -	17.0	17.1

3. **Transplantation.** Confirmation of the results of castration are yielded by transplantation experiments, among the most satisfactory of which are those of Marshall and Jolly. They showed that ovaries might be removed from dogs and rabbits, and that if part of one were transplanted in some suitable tissue, such as the kidney, all its tissues may survive and that no atrophy of the uterus occurs. Not only so, but ova are formed and œstrus may occur. Similar results are recorded in the human female. Casalis, quoted by Marten, describes a case in which the ovaries and appendages were removed for inflammation, and the left ovary transplanted on the left border of the uterus. Two and a half months after, menstruation was regular. The ovarian body could be felt on examination.

The cases which have been recorded in which transplantation of the ovary from one woman to another, from whom the ovaries had been removed, was followed by a subsequent pregnancy, are more probably due to incomplete removal of the original ovaries than to successful grafting of the foreign ovary.

Marshall and Jolly found that homoplastic grafts—*i.e.* grafts into the same animal—are more successful than heteroplastic grafts, and that grafts from nearly related animals—*e.g.* sisters—are more successful than from less nearly related.

The observations of Steinach on rats, in which ovarian tissue was transplanted into young castrated males, seem to show that the ovary exercises a marked influence upon the soma. He found the characteristic slight bony development, the growth of the finer hair of the female, the development of mammæ and nipples, and the appearance of two peculiar female reflexes—(1) "The tail erect reflex" and (2) the peculiar kicking guarding reflex to keep the male off before the full development of œstrus. These feminised rats were followed by males as if they were female.

He states that the interstitial cells alone are sufficient to bring about these changes, since all follicle cells in the grafts may atrophy.

These experiments of Steinach suggest that in the ovaries, as in the testes, the interstitial cells are the structures which play the active part in yielding the internal secretion, and results obtained by Louise M'Ilroy in this laboratory support this conclusion.

Apart from Steinach's work, the evidence of the part played by these ovarian interstitial cells is by no means so conclusive as that regarding the cells of Leydig in the testes.

Bouin and Ancel and Villemin have studied the influence of X-rays upon the ovaries, and state that the follicle cells are destroyed, but that the interstitial cells are increased, and that this condition is accompanied by an atrophy of the uterus similar to that produced by complete ovariotomy.

Louise M'Ilroy informs me that in some of her cases of ovarian grafts, with absence of any atrophy of the uterus, all the follicle cells had disappeared and only interstitial cells remained. This appears to bear out Steinach's results. The question certainly requires further investigation.

II. The Influence of the Gonads on the Course of Pregnancy. With the escape of the ovum from the Graafian follicle, which must precede pregnancy, the follicle undergoes certain changes to form the corpus luteum.

The old view that a hæmorrhage occurred into the follicle, and that the clot was gradually invaded by the cells of the zona granulosa or theca interna which removed the shed blood, has been disproved by the work of Sobotta on the corpus luteum of the mouse. He shows that hæmorrhages do not occur; and recent work on the human ovary seems to indicate that here too the essential change is a great proliferation of the cells of the granulosa to completely fill and distend the follicle with peculiar luteal cells—large cells containing fat droplets and pigment, and resembling the interstitial cells of the ovary. When pregnancy supervenes, the corpus luteum undergoes very much more marked development than when pregnancy does not occur.

Fränkel found that in the rabbit castration early in the pregnancy leads to abortion, and further that the same result might be obtained by destroying the corpora lutea by cauterising. He came to the conclusion that the corpora lutea exercise an influence in preparing the uterine mucosa for the embedding of the ovum and, pushing the analogy, he maintains that the corpora lutea of menstruation also act upon the uterine mucosa.

Marshall and Jolly confirm Fränkel's results that castration early in pregnancy in rats and dogs leads to abortion. They did not attempt to destroy the corpora lutea, and came to no definite conclusion as to whether the luteal cells are the active part of the ovary.

One of the most direct pieces of evidence in favour of the influence of the corpus luteum is that afforded by Leo Loeb, who found in rabbits and guinea-pigs, that, after ovulation and copulation, impregnation being prevented by afterwards ligaturing the Fallopian tube, if the uterine mucosa was irritated by cutting through the wall, growths of the nature of deciduomata—of placental tissue—occurred and persisted for ten days.

Martin has also produced these in rats in a very interesting manner. Ovulation and œstrus occur in these animals, immediately post-partum. Two to nine days after, *without* impregnation, the uterus was incised, and in some cases deciduomata developed and corpora lutea were found in the ovaries.

Prenant (1898) maintained that the corpus luteum acts by suppressing the ovarian activity and hindering ovulation during pregnancy. In support of this theory is the observation that in the cow, when a corpus luteum persists, œstrus does not occur. On removing the corpus luteum it does occur. Against this there has been cited the fact that in the mouse the corpus luteum persists into the next pregnancy. But this hardly tells against Prenant's theory, for structural persistence is no proof of functional activity.

The experiments of Leo Loeb in guinea-pigs give some support to Prenant's theory. He allowed copulation in sixty-three animals to fix the date of ovulation, but afterwards ligatured the Fallopian tubes and so prevented the onset of pregnancy. The formation of corpora lutea was demonstrated by microscopic examination, and it was found that few ovulated within sixteen or eighteen days. In forty-five, he attempted to remove the corpora lutea, and he succeeded in twenty-three. Twenty-two of these ovulated within twelve to sixteen days.

The fact that in rabbits œstrus may occur during pregnancy has been urged against this view. The condition is so rare as to justify the conclusion that it may be due to abnormal changes in the corpora lutea.

III. The Influence of Gonads on the Mammary Gland.—1. Development of the Mamma. One of the most characteristic developments in the female is the mammary gland. This structure appears in the fœtus in both sexes, but while in the male it normally undergoes no development, in the female, at the onset of puberty, it markedly hypertrophies.

That its growth is connected with the development of the ovaries is shown by the fact that, after early ovariotomy, it does not occur.

Further, the enlargement which occurs during œstrus, indicates an ovarian influence.

2. **Milk Secretion.** While the action of the ovarian gonadin explains the growth of the gland, the cause of the onset of its secreting activity has proved a more complex problem to solve.

Starling and Lane-Claypon have experimented on virgin rabbits by injecting extracts of rabbit fœtuses, ovaries and uterine mucous membrane, and they found that in certain cases at least the fœtal extracts lead to an hypertrophy of the gland.

This observation has been confirmed by Biedl, by Konigstein, and by others.

That the placenta yields an internal secretion acting on the glands to stimulate them has never been proved. Hence it must be admitted that the fœtus may yield something acting in this way. But the cause of secretion is not explained by this. For secretion becomes active *after* the expulsion of the fœtus and placenta.

It seems to me that a more probable explanation is that, when the young are discharged, the supply of material, which has hitherto been passing from the mother to the young, is suddenly left in the maternal blood, and that this—which is practically a fœtal extract—is a stimulant to milk secretion.

Opposed to the view that an internal secretion from the fœtus is the essential stimulus to milk secretion, is the well-known fact that some bitches some weeks after œstrus without impregnation secrete milk. I have seen a fox-terrier bitch suckle pups in this way.

Again, in some young children, irrespective of sex, secretion of milk may occur.

That milk secretion is not determined by the ovarian internal secretion seems to be indicated by the observations of Marshall and Jolly, that ovariotomy late in pregnancy does not interrupt gestation and does not interfere with milk secretion and suckling.

It is usually stated that the possibility of a nervous reflex being involved is excluded by the observations of Goltz and Ewald that a bitch, with complete transverse section of the cord in the back, can not only become pregnant and bear young but can suckle them. This, however, is no proof of the absence of a spinal reflex.

Several cases have been reported, both in the human subject and in lower animals, where continued irritation of the nipple by sucking has induced a secretion of milk in virgin animals.

The only possible explanation of this seems to be that a direct nervous reflex is involved, the only other possible explanation being that the continued stimulation with its accompanying vaso-dilatation leads to an increased formation of some internal secretion of the mammary gland which acts as a direct chemical stimulant to milk secretion.

The action of a nervous reflex by no means excludes the possibility of the action of a chemical stimulant, and in suckling probably both these factors play a part, the chemical products fortifying the nervous action. Hence the great abundance of the milk production in normal lactation where both factors are brought into play.

IV. Influence of the Gonads on Œstrus.—(A) In the Male.—The enormous hypertrophy of the testes which precedes the onset of œstrus in the male of many species of mammals and birds, and the failure of œstrus to develop after removal of the gonads, clearly indicate that the onset of the condition is determined by increased activity of the testes. What the causal factor of this great cyclic change is we do not know, but it seems primarily to involve the interstitial cells. In birds the testicular change seems to precede any somal change, and before the breeding plumage and the breeding instinct have developed the testes have grown many fold.

With the growth of the testes the whole character of the bird changes. In fact, birds and mammals with well-marked œstrous cycle undergo a constant transition from the state of the apathetic eunuch to that of energetic manhood.

(B) In the Female. The fact that œstrus occurred in Marshall and Jolly's animals with transplanted ovaries disposes of the neurogenic theory of its onset, and indicates that it is due to a secretion from the ovaries. It supports the evidence afforded by Ewald and Goltz' dog from which the lumbar part of the spinal cord was removed and which still manifested "heat" and became pregnant, and it is much more convincing than the observation of Goltz that a bitch with the spinal cord divided in the back developed œstrus and became pregnant, or the fact that Sherrington's spinal bitch showed the regular onset of heat, or Brachet's well-known case of a woman with complete transverse lesion of the cord who became pregnant.

The enormous growth of the ovaries in animals with a well-marked sexual cycle, as in such birds as the sparrow before the breeding season, taken in conjunction with transplantation experiments proves that the onset of œstrus is determined by the gonads. That this influence is a very profound one is perhaps best seen in birds in which, not only is a special breeding plumage developed, but the extraordinary nidifying reflex is produced and the whole character and habits of the bird are changed. But we have as yet no definite knowledge of whether the interstitial cells play the most important part or whether the process is determined by the follicle cells, or whether—which is probable from their common origin—they undergo simultaneous increase.

That the maturation of Graafian follicles is not essential to the onset of œstrus has been shown by Marshall, who destroyed the ripening follicles with thermo-cautery without stopping the onset of heat.

This conclusion is further supported by the fact that bats have their œstrus in autumn when they copulate, but the ova in the follicles do not ripen till spring when they are fertilised.

V. The Influence of the Gonads on Metabolism. The structural and functional changes produced in animals by variation in the activity of their gonads and by removal of these structures is simply an expression of the altered metabolism which is the basis of every physiological reaction.

The subject has been chiefly studied in two ways. By the investigation of (*a*) the effects of castration, (*b*) the effects of administering extracts of the gonads to castrated animals.

So far as I am aware no attempt has been made to study the metabolism in the anœstrous and in the œstrous condition of animals, although observations are recorded upon the changes in metabolism in the non-menstrual and menstrual states of women.

The most general effect of castration is the tendency to deposition of fat—although this is not universal.

Loewi and Richter found a decrease of 14 to 20 per cent. in the respiratory exchanges of both male and female dogs after castration, and they state that the administration by the mouth or subcutaneously of ovarian and testicular extracts to these animals raised the metabolism by 30 to 50 per cent., while the administration to normal animals has not this effect.

Lüthje, in one experiment on a dog and one on a bitch, could not confirm this. His work, as well as that of others, affords no evidence that the protein metabolism is modified by the gonads.

The evidence as regards the influence on the excretion of calcium and phosphorus is conflicting. Neumann and Vas found a decrease on castration and an increase on administering ovarian extract. But Lüthje failed to find any changes.

More work is wanted upon the subject, but the changes, if any, must be so small that day by day observation probably will not reveal them, and comparisons over periods of at least a week or a month will have to be made.

The influence upon the calcium and phosphorus metabolism is of moment on account of the possible association of the ovaries with osteomalacia and the reputed benefit of castration in this condition.

VI. On the Vascular System. The relationship of vascular changes to the sexual functions is very marked and leads to the consideration of whether there is any evidence that these changes are determined or controlled by the products of the glands.

That dilatation of the vessels of the genitalia is directly produced by nervous impulses is shown by the effects of electrical stimulation of the nervi erigentes.

Simpson and Marshall found that while stimulation of the nervi erigentes in the normal dog leads to erection of the penis and ejaculation of semen, stimulation in castrated animals causes comparatively slight congestion.

These results support the view that the gonads have an influence in facilitating the action of nerves upon the vaso-dilator mechanism.

So far, we have considered the influence of the gonads upon the soma. The question now arises, **Can the condition of the soma influence the gonads ?**

Two distinct problems are here involved :

1st. Can the soma so influence the gametes as to determine the sex of the individual into which they will develop ?

2nd. Can it influence the growth and maturation of the gonads ?

1. Influence of the Soma on Sex Determination of the Gametes. The work of older investigators such as that of Born and of Yung upon tadpoles, of Treat upon caterpillars, and of Nussbaum upon the rotifer, hydatina, seemed to give a positive answer and to show that sex might be determined by the nutrition of the body of the parent.

But careful examination of this work and the repetition and extension of the investigations have not afforded confirmation, and tend to show that sex is primarily determined at the time of conjugation of the male and female cells by the character and distribution of the chromosomes, usually of the male cell.

It has been found that in many classes of insects, in many millipedes, worms and vertebrates, in addition to the ordinary chromosomes, others exist which may be called the *x*-chromosomes. In the female cell they are paired, and, in the process of reduction, one thus lies to each daughter cell. But in the male cells they are unpaired, so that, in the process of reduction, the spermatids are of two kinds, one containing the *x*-chromosome, one without it. Impregnation of an ovum by the spermatozoon which contains the *x*-chromosome leads to the production of a female, impregnation by that which does not contain an *x*-chromosome to a male. In this way the proportion of males and females produced is equal.

While this may be taken as a statement of the typical cases of sex determination, the problem may be complicated by the development of other forms of chromosome and by other modifications. But in all these cases the general rule seems to apply, that the predominant factor in the determination of sex is the distribution of chromosomes in the gametes.

If this is so, the possibility has to be considered, whether there is any evidence that the distribution of chromosomes may be so modified as to produce an alteration in the sex-producing potentiality of the gamete. There is considerable evidence in favour of this.

Thus, in the females of the nematode *Rhabdonema nigrovinosum*, certain sex cells lose an *x*-chromosome and become spermatogonia.

In Pteropods two chromosomes in the cells of one part of the sex gland may experience a decrease, and thus the chromatin, which first possessed a male character, may become female in type.

Again, after the parasitic castration of the male crab described on p. 143, not only are the somal characters changed, but the gametes develop into ova.

Such effects upon the alteration of sex potentiality by alterations in the chromosomes seem very clearly to indicate that there is no essential and fundamental difference between male and female gametes, and that the one may undergo change into the other.

These effects upon the chromosomes must be exerted through the protoplasm of the gametic cells, and there is some reason to believe that this may be modified by changes produced in the soma. The effect of low temperature in increasing the proportion of males to females in frogs has been recorded by Hertwig.

It must, therefore, be admitted that, while as yet no positive evidence is forthcoming, there is a probability that the sex determination of the gametes may be influenced by the state of the soma.

The progress of parthenogenesis in various invertebrates throws light upon the question of the influence of the soma on the gametes. In many forms—*e.g.* aphis, the tree louse, daphnidæ, the water fleas, and hydatina, a rotifer—oöcytes develop, which form only one polar body and which, without impregnation, develop into another generation of females reproducing in the same parthenogenetic manner. But, in the course of time, eggs are produced in which two polar bodies are formed and which must be fertilised by the spermatozoa. Male forms, bearing spermatogonia, are also produced. Although Weismann has maintained that this variation in the character of the gametes produced is a purely cyclic one, the investigations of a large number of independent observers seem clearly to show that it is modified by surrounding conditions, such as the character of the food supply and variations in temperature which possibly act by modifying the food supply.

Thus, in a recent paper, Grosvenor and Geoffrey Smith show very clearly that the sexual cycle of *Moina rectirostris* may be materially altered by external conditions. Normally the female, which results from the impregnated egg, produces in its first brood only parthenogenetic females, but in each succeeding generation, along with parthenogenetic females, ordinary males and females. In this investigation the production of males was taken as a measure of the production of sexual forms, and it was found that, by isolating the animals and keeping them at a high temperature, the production of such sexual form was entirely suppressed. Whether this is the result of modified food supply is not decided. But it shows very clearly that some influence, probably acting through the soma, checked the normal development of those forms of ova which produce sexually distinct creatures.

Agar's observations on *Simocephalus vetulus*, although not specially undertaken to elucidate the influence of external factors upon the gametes, show that by suitable feeding parthenogenetic reproduction without the appearance of sexual forms (males) may be continued through many generations.

It may be maintained that these altered external conditions act directly on the gametes. But the fact that such a chemical change can produce a modification renders it highly probable that changes in the chemical products of the metabolism of the soma can act in a similar manner.

While recognising that the sex of the offspring is determined by the distribution of chromosomes in the conjugating gametes, it must be admitted that this distribution seems to be capable of alteration through the influence of external conditions, and probably through alterations in the soma, and that the character of the nuclear divisions preceding the development of the ovum into a parthenogenetically developing egg, or into an egg requiring fertilisation, may be modified in a similar manner.

2. Influence of the Soma on the Maturation of the Gonads. That the soma acts in this way is shown very strikingly by the influence of feeding in determining the growth of the gonads in bees. From the great number of potential female bees—the workers—a few true functionally active females—the queens—are developed by special feeding.

The view has sometimes been expressed that a factor in the determination of the onset of the activity of the sexual organs is the nutrition of the soma. The stag, for instance, ruts when the greatest store of fat has been accumulated. But, on the other hand, many animals manifest their sexual activity at a time when the body is poorly nourished. Thus the breeding season of the frog is immediately after hibernation.

A most striking example of the independence of the development of the sexual organs upon the nutrition of the body was brought under my notice three years ago, when a male salmon was sent to me in November with the testes so ripe that the fish had been used for artificial impregnation, and yet the animal had remained in the spawning tank for twelve months without any food, and was reduced to a condition of extreme emaciation.

In the female, the activity of the ovary may undoubtedly be stimulated by the condition of the soma. This is well seen in the common experience of the poultry farmers. It is also well known to the sheep breeder that when the ewes have been poorly fed at pairing time the proportion of twin lambs is small.

How far this is a simple nutritional influence upon the gonads is not easily decided. It may be an action through some of the other regulator structures of the body, such as the thyroid, inter-renals or pituitary.

Summary. We have seen that gonads are formed in the genital ridge by the ingrowth of the mesothelium, and that the mesothelial cells differentiate into the true gametes, into ancillary cells lying with the gametes in the seminal tubules of the male and in the Graafian follicles of the female, and into interstitial cells.

The effects upon development and growth, of removal, of precocious development, of transplantation, of administration of extracts, and of ligature of the ducts (in the case of the testes) have been described.

The conclusion has been arrived at that male and female gonads yield an internal secretion which acts upon the metabolism of the body to stimulate it in each sex in a specific manner, and that almost certainly this internal secretion is a product of the interstitial cells. A consideration of the relationship of these interstitial cells to the activity of the gonads has led to the conclusion that they may be regarded as a middleman between soma and gametes, and that it is through them that the soma and gametes influence one another. No evidence has been found as to whether this action on development and growth is directly upon the tissues or through the nervous system. The action of the gonads upon the onset of œstrus and upon the vascular system has been described, and the special influence of the interstitial cells has been indicated. In the female the relations of the gonads, and more especially of the special development of the thecal or ancillary cells of the corpus luteum, have been discussed. It has been shown that there is good evidence that the luteal cells yield a secretion which plays an important part in the embedding of the ovum in the uterine mucosa and in the early nutrition of the embryo. The importance of the ovarian internal secretion in determining the development of the mammary gland has been described. On the production of milk secretion the probable influence of the nervous system on the one hand, and of the chemical stimulation resulting from the separation of the fœtus from the mother and the accumulation of products hitherto passed out to the fœtus, have also received consideration, and evidence has been adduced that both play their part in normal lactation.

The discussion of the question of whether the soma acts upon the gonads has led to the conclusion that, while both the determination of the sex potentiality of the gametes and the ripening of the gonads is a cyclic phenomenon depending upon hereditary inertia, there is good evidence that both may be modified by the external changes acting through the soma.

II. THE INTER-RENAL TISSUE.

Development. Before the definite development of the gonads, an ingrowth of the mesothelial cells on the genital ridge occurs and gives rise to the structures which may best be called the Inter-renal Bodies.

In fishes these bodies remain separate and independent, but in higher vertebrates they become more closely related to the main mass of chromaffin tissue on each side, which forms the medulla of the supra-renal body, and in mammals they completely enclose this forming the cortex supra-renalis. The cells of this tissue are large with distinctly reticulated protoplasm, and strongly resemble the interstitial cells of the testes and the cells of the corpora lutea of the ovaries. Like these, they contain granules of a lipoid nature which stain red with Scharlach Rot but tend to stain brown with osmic acid. Pleçnik states that in sections kept for a long time in Müller's solution and stained by Weigert's chrom-hæmatoxylin method, these granules are coloured blue, as are also the fat granules of the interstitial cells of the testes. He says that these granules may be detected in quite young human embryos and that they increase till about the end of the first year. Brown pigment granules are also found, but these are absent in the embryo and increase as age advances.

Elliott and Armour have investigated the later stages of the development of this tissue in the cortex supra-renalis of man. They find that it first consists of columns of cells lying closely round blood-vessels and free of lipoid granules. Round the surface of this mass of cells smaller cells develop and in these lipoids make their appearance. At the time of birth the supra-renal body is nearly as large as the kidney, and it consists chiefly of the cells first described. After birth the cells at the surface increase and the original cells degenerate. So far as I am aware, no similar series of changes has been described in any other animal, but the subject requires investigation.

Structure. In the adult cortex supra-renalis the inter-renal cells are arranged in three zones differentiated from one another chiefly by the distribution of the fibrous tissue. The outmost, **zona glomerulosa,** has somewhat rounded or fan-shaped spaces filled by cells which are generally clear and more free of pigment than the deeper cells. They often show mitosis. The mid-layer, the **zona fasciculata**, consists of cells with the most typical character of inter-renal tissue arranged in long columns radiating from the centre. The inmost layer, the **zona reticularis**, is looser and the spaces more irregular. The cells are again clearer and they are less closely packed together. This zone tends to invade the chromaffin tissue of the medulla and to be invaded by it.

Physiology. The close association of the inter-renal and chromaffin tissue in higher vertebrates led to the formulation of the theory that the former in some way prepares a precursor of adrenalin for the latter. The complete separation of the two tissues in fishes, and the absence of positive evidence of this ancillary action, renders this theory untenable.

The old view—a view applied at one time to every tissue the function of which was not elucidated—that it acted as a de-toxicating organ, neutralising hypothetical poisons, hardly requires consideration. The fact that the lipoids of the cortex, like lipoids elsewhere, combine with many chemical substances to neutralise their activity is no proof that in the living cortex they act in this way.

1. **Removal**. The close association of the inter-renals with the adrenal system in all vertebrates above fishes makes it very difficult to study the effect of simple removal of the former, because the latter is so apt to be involved.

Biedl has taken advantage of their complete separation in fishes to remove the inter-renals of selachians, and he finds that the animal gradually becomes weaker, refuses food and finally dies in fourteen to eighteen days. In one skate, where a piece of inter-renal of about the size of a pea had been unintentionally left, muscular weakness and death did not supervene, and the animal lived for more than four weeks and was finally killed. In this animal, and in four others which died in spite of small pieces of the inter-renal being left, a regenerative process was found in progress.

Pettit and Vincent attempted the same operation in eels but did not get these results. Giacomini however has shown that in eels there is not only the posterior inter-renal, which Pettit and Vincent removed, but also an anterior one, which they did not interfere with. The activity of this is probably sufficient to maintain life.

It has for long been known that complete removal of the whole supra-renal of mammals, unless when well-developed accessory organs exist, leads to death, and Biedl's experiments appear to indicate that, whatever part is played by the central or adrenal part, the cortical or inter-renal part is an organ essential for the maintenance of life.

2. **Transplantation.** The results of transplantation of the supra-renals help little in arriving at a conclusion as to the mode of action of the inter-renal system. Poll experimented upon rats and found that the inter-renal or cortical part alone survived. But, since in about 50 per cent. of rats accessory inter-renals are present, the fact that the animals lived was no indication that the transplanted cortex was the structure upon which the maintenance of life was dependent.

Haberer and Stoerk successfully transplanted both parts of the supra-renal. In these cases one supra-renal was left untouched. When it was afterwards removed the animal lived. But upon subsequent excision of the successful graft death ensued. Since both inter-renal and chromaffin tissue were present in the graft, no conclusion could be drawn as regards the special action of either.

3. **The injection of extracts** of the inter-renals of fish were found by Vincent to be without effect on mice, while injection of the adrenals produced the marked symptoms which follow the administration of extracts of the medulla supra-renalis of other vertebrates.

These ordinary methods of experiment have done little to elucidate the functions of this tissue. The presence of a certain amount of the structure seems to be essential for the maintenance of life, but how it acts we do not know.

4. **Relation to the Gonads.** Its relations with the gonads gives a hint as to a possible action.

The common source and the histological similarity of the inter-renal cells and the interstitial cells of the gonads have been already indicated. Subsidiary masses of inter-renal tissue or inter-renal "rests" are very common, and especially common in the epididymis testis. Kirkbride found such rests in a considerable proportion of the testes examined, eight out of twenty-seven, while Wiesel states that they are present in 76.5 per cent. of the cases examined.

Marchand has also described them in the broad ligament of the female.

The recent careful investigation by Kolmer on the changes in the cortex in the guinea-pig throughout life tends to confirm the close relationship of the structure with the gonads. He describes the suprarenal in young animals of both sexes as the same. "Siderophilous" bodies appear in the cells, and similar bodies are also found in the cells of the corpus luteum, in the interstitial cells of the ovaries of pregnant and puerperal guinea-pigs, and in the interstitial cells of the testes.

In the female the cells of the deeper part of the zona fasciculata are loaded with lipoids.

During pregnancy a breaking down of the siderophilous cells of the zona reticularis occurs which leads to the escape of pigment and to the formation of spaces. The cells are afterwards regenerated from the periphery where numerous mitotic figures appear, thus recalling the ante-natal changes described by Elliott and Armour in the fœtus.

Additional work upon these lines throughout the œstrous cycle is urgently required.

Glynn gives a most valuable account of the evidence of the relations of the adrenal cortex to the gonads. From the consideration of the experimental evidence and of the large number of cases which he has collected, he concludes that the enlargement of the cortex which occurs during breeding, pregnancy, and after castration, and the small size in deficient sexual development indicate a relationship between the cortex and the sex characters. He finds that hyperplasia in females is associated with diminution of female characters and with the development of male characters, and that premature development of sex characters in the male may be associated with tumours of the cortex.

In children and young women where sex abnormalities appear, there is usually unilateral malignant tumour formation in the cortex supra-renalis.

In pseudo-hermaphroditism, abnormalities of the supra-renals, when present, are bilateral, and are of the nature of a hyperplasia or of cortical rests. This probably indicates concomitant abnormality of growth in two structures derived from a common source.

As Glynn points out, it is possible that the cortex supra-renalis may play a part in determining the growth of the gonads, since it is developed in man at the fourth week of intra-uterine life, while the gonads are not definitely developed till the third month.

These observations show the close connection of cortex and gonads, but they leave unsolved the problem of the nature of this connection. Whether these structures functionate together, or whether they react on one another, or whether together they act to produce the various manifestations of the sexual cycle, we cannot at present say.

The consideration of the physiology of the supra-renals cannot be left without a brief reference to *Addison's Disease*, a condition described in 1855 and associated with destructive lesions, usually tubercular, of the supra-renal bodies.

The most marked symptoms are great muscular weakness, gastro-intestinal troubles, emaciation and a curious bronzing which generally begins in patches on the mucous membrane and extends to the skin.

The muscular weakness and emaciation are probably similar to the condition produced in lower animals on removal of the supra-renals, and, if these are to be associated with loss of cortex as indicated by Biedl's experiments on the skate, we should be inclined to refer the symptoms to loss of cortex from the tubercular lesion. The post-mortem reports on cases are far from satisfactory, some observers describing destruction of the cortex, others of the medulla, most of both.

There seems little evidence that the loss of medulla has any causal relations to the symptoms, for there is no evidence that adrenalin exercises any tonic effect upon skeletal muscle.

Summary. The cells of the inter-renal tissue and of the gonads have been found to have a common origin, and the morphological resemblance between the cells of the former and of the interstitial cells of the latter and of the corpus luteum, has been indicated.

The difficulty of investigating the functions of this tissue apart from the chromaffin tissue, and the way in which Biedl has taken advantage of the complete separation of these tissues in elasmobranch fishes to effect its removal, have been described, and it has been seen that Biedl's results point to the inter-renal portion of the supra-renal as being the part which is essential to life, although they give no indication of how it acts.

The relationship of the tissue to the gonads, the changes described by Kolmer throughout the œstrous cycle, and the co-related changes in the gonads and inter-renals in physiological conditions such as pregnancy, and in various abnormalities of the sexual organs, have been considered. The evidence has been found insufficient to show whether the changes in one tissue are causal to those in the other, or whether they are not merely concomitant. The facts recorded suggest the possibility that the cells of the inter-renal tissue are part of the same system as the interstitial cells of the gonads and act with them.

SECTION IV.

THE INTERRELATIONSHIPS OF THE ENDOCRINOUS GLANDS.

In the previous sections the action of the various regulators of metabolism, and the way in which each exercises its effects on the development, growth and metabolism of the body have been considered. Evidence has been forthcoming that they interact upon one another.

The more difficult problem has now to be faced. Is their action so co-ordinated that each produces its proper effect, neither more nor less, in normal metabolism and growth? Is each simply controlled by the nervous system? Or, do the various structures, through their products, regulate the effects of one another?

On these problems the effect of grafts and the administration of extracts seem to afford some evidence. The fact that a graft keeps up the balance between the various endocrinous organs, and prevents any disturbance of the body, is in favour of the view that the interaction is primarily a chemical one so far as the production of the secretion is concerned, and not an indirect one through the nervous system. Although it may act upon other glands through nerve endings, the activity of the graft itself can be regulated only by the influence of the products of other tissues passing to it in the blood.

In investigating these questions, the interpretation of the results of removal or disease of one organ on another is often very difficult, because it is not always the same. Thus, while in most cases of the hypothyroidism of cretinism, the anterior lobe of the pituitary is enlarged, cases have been described where no such enlargement was present. Is the evidence of compensatory hypertrophy of the pituitary on this account to be rejected? To my mind these apparently opposing findings in cretins are not an argument against the association. If the compensatory hypertrophy does not occur, the condition of the individual probably is worse than when it does occur. When studying the action of testes and thymus on growth, I found that one guinea-pig in my series, after removal of the thymus, hardly grew at all, although remaining quite well and active. When it died at over four months old it was like an animal about a fortnight old, and the testes were in size and structure those of an animal of the same age. They had undergone no compensatory hypertrophy, as they usually do, and the result had apparently been the arrest of growth which occurs when thymus and testes are removed together.

Again, in assessing the functional activity of an organ, the absence of definite structural change cannot be taken as proving the absence of change in activity, while conversely marked structural change may be unaccompanied by change of function. The most profound disturbances in metabolism may occur without producing structural alteration. On the other hand, extensive structural changes, especially of the connective tissue framework of an organ, may occur without its functional activity being seriously implicated, *e.g.* in the liver. And the evidence we possess is very clear that each one of these endocrinous structures is more than sufficient to perform its function, and that each has a wide safety limit so that, *e.g.* one-eighth of the thyroid tissue is sufficient to prevent the onset of symptoms of hypothyroidism, and less than one-fifth of the pancreas prevents the development of diabetes.

The possible complementary action to one another of these structures creates a further difficulty in investigating their functions. Thus, in some species, in early life the gonads can so effectually compensate for the loss of the thymus as altogether to mask the effect of its removal, and the conclusion might thus be arrived at that the thymus has no effect upon growth and development. A similar compensatory action is seen between other structures, *e.g.* the thyroid and pituitary.

An alteration in the activity of any one of these structures may lead to changes, not only in those it has direct relationships with, but in others with which these associated organs are more especially connected. Thus, decrease in thyroid activity may lead to decrease in the gonads, and this may lead to compensatory hypertrophy of the thymus. It is, of course, also possible that the thyroid and thymus have a direct antagonistic action, and that decrease in thyroid activity may thus lead directly to thymus hypertrophy.

As yet, the knowledge we possess is all too inadequate to allow us to formulate with any precision the interrelations of the various endocrinous structures with one another. All we can do is, in a tentative manner, to express the probable interrelations, not as a contribution to permanent knowledge but rather as a guide to further investigation.

I have endeavoured to reduce this to the form of a series of charts or diagrams. These may well be a grotesque parody of what will ultimately be found to be the relationship of the activities of these organs. They are probably as near the truth as these quaint ancient maps of the Indies with their "here be much gold" scrawled across them which served as the charts of our forefathers, and if, like them, they merely indicate the direction which further investigation should take and suggest lines of attack, they will have served their purpose.

In dealing with the functions of each of the various structures, its probable relations with others has been considered, but this question will now be more fully dealt with.

THE GONADS.

The direct and profound action of the endocrinous secretions of the gonads upon the development of the soma has been considered. Every tissue of the body is played upon by them.

How far is their action facilitated and how far is it checked by other endocrinous organs?

The **thymus** undoubtedly supplements the action of the testes. We do not yet know if it acts in the same way as regards the ovaries. It thus seems to exercise a checking action on the growth of the male gonads, and they in their turn act reciprocally upon the thymus. But, as we have seen, they have a common action in stimulating the growth and development of the tissues, and the hypertrophy of one, caused by the removal of the other, is a compensatory hypertrophy (Figs. 4 and 7).

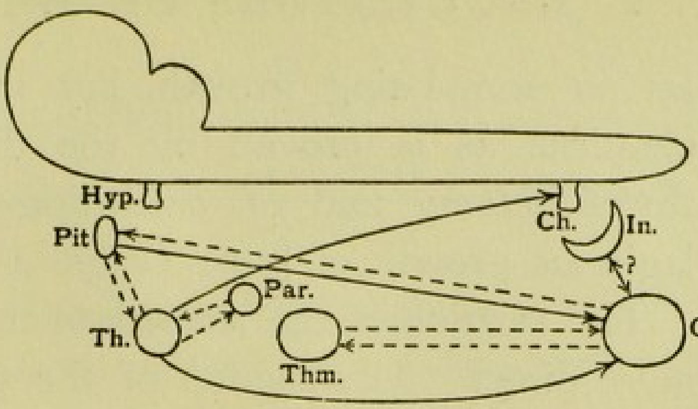
The **thyroid** on the gonads is also fairly direct but of another kind. Its removal checks their growth. Castration, however, does not appear to cause any marked change in thyroid activity, although the old observations of Meckel that the thyroid increases during menstruation, and some quite recent work by Engelhorn abstracted in the *Zbt. f. Phys.* 1913, Bd. 26, p. 1210, suggest some reciprocal action. The action seems, however, to be rather from thyroid to gonad than the reverse. Both

FIG. 4.—To show the probable influence of the various endocrinous structures on one another. The following explanations apply to this and to the three succeeding figures.

——————— = stimulation.

. . . . = inhibition.

The arrow indicates the direction of action.



Hyp. = Hypophysis.	Pit. = Pituitary.	Th. = Thyroid.
Par. = Parathyroid.	Thm. = Thymus.	In. = Inter-renal.
Ch. = Chromaffin System.	G. = Gonads.	Pan. = Pancreas.
Art. = Artery.	B. = Bone.	M. = Muscle.

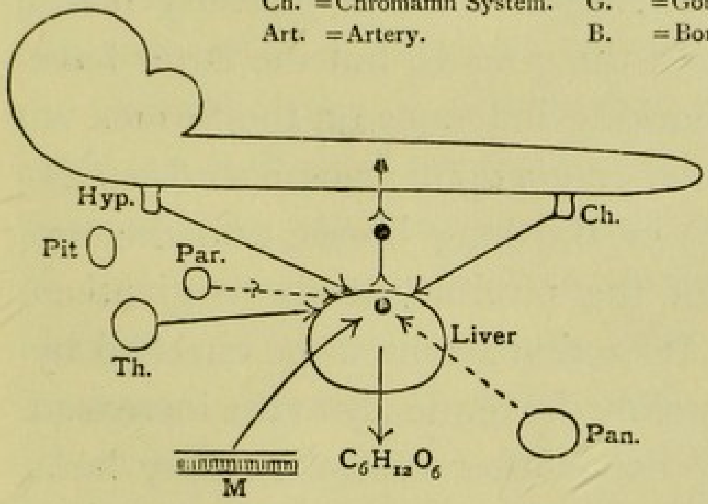
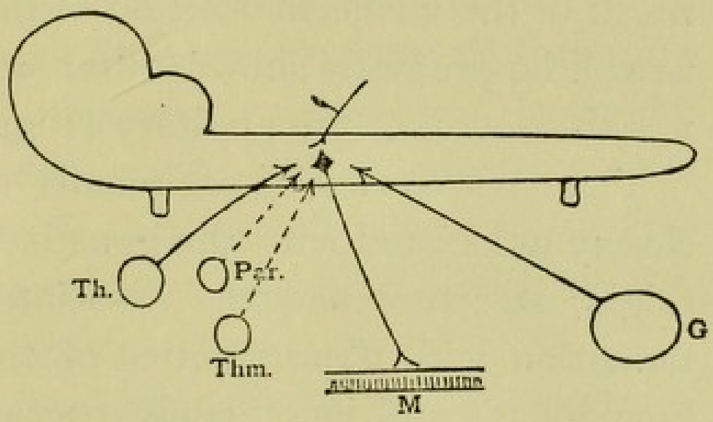


FIG. 5.—To show the probable mode of action of the various internal secretions on the mobilisation of sugar in the liver.

FIG. 6.—To show the probable mode of action of certain of the internal secretions upon the spinal reflex arc.



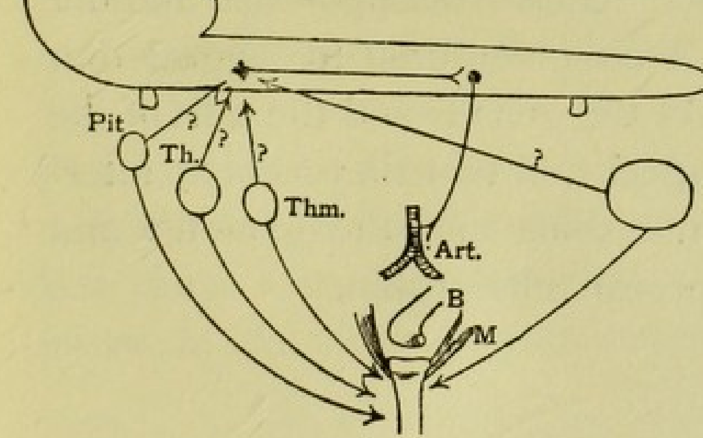


FIG. 7.—To show the probable mode of action of the internal secretions on the growth of muscle and of bone and other connective tissues. The possibility of this being of a vaso-motor reflex mechanism is indicated by lines marked ?.

act in stimulating growth, but the action is not identical, as is proved by the different effect of thyroidectomy and of castration upon the cartilaginous growth of bone (Figs. 4 and 7).

The relation of the pituitary to the gonads is even more direct. Destruction of the pituitary leads to atrophy of the sex glands, while castration causes hypertrophy of the pituitary. The pituitary has a stimulating action on the gonads, but the latter have an inhibitory or checking influence on the former.

Both have a similar action upon growth, and especially on the growth of the long bones, and the uncontrolled action of the pituitary leads to giantism and acromegaly. Its action seems to be checked by the gonads, and possibly the tendency to the increased length of the long bones after castration may be a result of the unchecked action of the pituitary. But, as will be presently shown, other structures also control the action of the pituitary (Figs. 4 and 7).

That the cortex supra-renalis or inter-renals are closely associated with the gonads is shown by their origin, structure and the association of their malformation with abnormalities of the genitals. But how gonads and inter-renals react upon one another is not yet known. I have ventured to suggest that the interstitial cells of the gonads and the cells of the inter-renals are identical, and that they form an intermediary between the soma and the gametes and regulate their reciprocal relationship.

THE THYROID.

The relations of the thyroid to the **gonads** has been already dealt with.

Its most direct physiological relationship seems to be with the organ of similar origin—the **pituitary**. Removal of the thyroid leads to hypertrophy of the pituitary, and Cushing finds that in young dogs removal of the pituitary causes hypertrophy of the thyroid (Fig. 4). They thus exercise a mutual checking influence similar to that exercised by the thymus and gonads on one another. Their relation to the soma seems to be similar but not quite identical. Hyperthyroidism does not cause the increased growth of bone and connective tissue which follows excessive action of the pituitary. On the other hand, hypothyroidism causes the decreased development of bone in length, in spite of the compensatory hypertrophy of the pituitary. It would almost seem as if their action was co-operative, and that the pituitary is unable to manifest its full adequate effect without the coincident action of the thyroid.

Observations upon the effects of simultaneous removal of both structures should throw further light upon the relations of each to the growth and development of the body.

With the **thymus** the relations of the thyroid are less clear. Boccia states that no change could be found in the thymus after removal of the thyroid or parathyroid, or both of these structures. The findings as to the influence of removal of the thymus on the thyroid are contradictory. Klose and Vogt describe an hypertrophy, M'Lennan and others an atrophy.

The direct effects of hyperthyroidism produced upon the thymus by administering thyroid preparations does not appear to have been directly tried; but the offspring of guinea-pigs fed with thyroid were found by Hoskins to have the thymus enlarged. The enormous variation in the size of the thymus of guinea-pigs at the time of birth makes definite conclusions upon this point difficult.

In Graves' disease, generally recognised as a condition of hyperthyroidism, hypertrophy of the thymus is very frequent. The theory has been advanced that these two structures antagonise one another, and that when the thyroid hypertrophies in Graves' disease the thymus hypertrophies to check its action.

The action of these structures on the gonads seems to be in opposite direction; the thyroid stimulating their growth, the thymus checking it.

Accepting the results of Basch, and of Klose and Vogt, the action of thyroid and thymus upon the neuro-muscular mechanism is also an opposing one (Fig. 6). Hence it would seem that, at least during the period of growth, a balance has to be maintained between them in order that the action of each should be kept in check, so that the normal activity of the neuro-muscular mechanism should be maintained.

The experiments on tadpoles, showing that thyroid feeding stimulates development, while thymus feeding stimulates simple growth, also suggest an antagonism between the structures.

Little evidence is forthcoming as to the relations of the thyroid and **parathyroids**, and any conclusions must be based upon what is known of the different modes of action of the two structures. The parathyroids act upon the nervous system in somewhat the same way as does the thymus, and in this respect they are thus antagonistic to the thyroid. Further, it has been maintained that, while tolerance for glucose is increased by removal of the thyroid when sufficient parathyroid tissue is left, it is decreased if the parathyroids are removed. If this is the case, it also points to an antagonism. Various changes have been described in the parathyroids after removal of the thyroid by Vincent and others. But these, so far as they go, rather point to a compensatory hypertrophy than to identity of action.

The evidence of the relationship of the thyroid and **chromaffin system** to one another has been considered in an earlier chapter. Hypothyroidism leads to hypo-adrenalinæmia, while, in the hyperthyroidism of Graves' disease, an increase of adrenalin in the blood has been described. The same has been described after the injection of thyroid extracts. Hence it appears that the thyroid secretion acts as a stimulant to the chromaffin tissue, increasing the output of adrenalin.

Thyroid extract probably facilitates the mobilisation of sugar, and hence it seems to act not only as a stimulator of the chromaffin system, but also as a facilitator to the action of the adrenalin produced. This has, in fact, been used as an argument for its action upon the terminations of the true sympathetic system. It remains to be seen if the interesting observation of Eppinger, Falta and Rudinger that, after thyroidectomy, adrenalin has a less effect in causing glycosuria is true.

On the reciprocal action of the thyroid and **hypophysis** nothing definite is known. The similarity in the action of adrenalin and hypophysin suggest the possibility of a co-operative action between these structures.

That the thyroid acts upon the **pancreas,** the organ which plays so important a part in inhibiting the mobilisation of sugar, is indicated by the frequent occurrence of glycosuria in hyperthyroidism, by the modification in the character of the diabetes produced by the removal of the thyroid along with the pancreas, and by Lorand's observation that removal of the thyroid in a dog, in which pancreatic diabetes has been established, decreases the output of sugar (Fig. 5). The action of the thyroid on the pancreas may be a direct one, as is suggested by the observation that thyroidectomy is followed by hypertrophy of the islets of Langerhans. But such evidence cannot be considered as satisfactory or conclusive. On the other hand, it may be that the influence of both structures on the mobilisation of sugar is exerted through the terminations of the true sympathetic in the liver.

THE CHROMAFFIN SYSTEM.

The important interaction of the chromaffin system with the thyroid and pancreas in controlling the mobilisation of sugar in the body has been already fully considered. With the other ductless glands no direct relationships have been established (Fig. 5).

THE PARATHYROID.

About the relationship of the parathyroids to the other endocrinous structures very little is known. The fact that pregnancy accentuates the symptoms of hypo-parathyroidism suggests a relationship with the gonads. But the precise nature of this is not clear.

The neuro-muscular instability manifested in the muscular tremors which sometimes accompany the activity of the gonads possibly also indicate a relationship between these structures and the parathyroids. So far as I am aware, no observations have been made on the effects of removing either of these upon the condition of the other (Fig. 6).

The theory that they are merely part of the thyroid has been already considered. Morphologically they are of independent origin, and the mere fact that they undergo changes, with an approach in appearance to thyroid tissue, when the thyroid is removed, does not prove their identity.

Rudinger has developed the theory that thyroids and parathyroids are antagonistic, and believes that this explains the hypertrophy of each when the other is removed. He refers to the prejudicial effects of administration of parathyroid extracts in hypothyroidism, and to its beneficial effect in Basedow's disease. He also refers to the observation that adrenalin fails to produce glycosuria after thyroidectomy, but acts markedly after parathyroidectomy, and he believes that the one stimulates the sympathetic to mobilise sugar, while the other depresses it. These observations have not been fully confirmed, and his hypotheses cannot be accepted without reservation (Fig. 5).

As to the relationship between parathyroids and the **thymus**, the common origin of the two structures from the epithelium of the third and fourth branchial clefts, and the fact that at first they are alike, and that parathyroids occur in the thymus, are worthy of note. Further, the observations of Basch and of Klose and Vogt on dogs, seem to show that thymusectomy produces nerve symptoms not unlike those of parathyroidectomy (Fig. 6).

It seems at least possible that they may be part of one system, and that the thymus may develop and functionate during the early growth of the body, and that the action of the parathyroids may become prominent at a later date. Were this the case, we should expect to find the symptoms of parathyroidectomy less marked in very young animals. So far as I know, this is not the case.

The onset of symptoms resembling tetany in pups after thymus removal, at a time when the thymus has ceased to functionate, suggests the necessity of further investigations of the thymus of these animals for the parathyroid tissue which is present in the rabbit and cat. Matti failed to find it.

One observation which suggests a possibility of further work is Ott's finding that injection of pituitary checks the tetany of parathyroidectomy.

THE THYMUS.

Apart from its relations to the gonads and to the thyroid, the most intimate relation of the thymus appears to be with the **parathyroids.** More work upon this point is wanted, but it almost looks as if the parathyroids might, after sexual life is reached, take over a great part of the function of the thymus in its controlling influence on the neuro-muscular mechanism. No examination of the parathyroids in cases of early thymusectomy have, so far as I am aware, been recorded.

It is manifest that our knowledge of the interrelations of the endocrinous glands to one another is still very imperfect, but that this interaction is a matter of great importance in the regulation of metabolism. A large field of work is open to the physiologist, and results of interest should be obtained by the simultaneous removal of pairs of organs supposed to be related to one another.

SECTION V.

THE RELATIONS OF THE ENDOCRINOUS STRUCTURES AND THE NERVOUS SYSTEM.

In the consideration of the functions of the endocrinous structures, it has been shown that certain of them at least are to some extent controlled by the nervous system, and that some exercise their functions by acting through the nervous mechanism.

It is now necessary to summarise the evidence as regards the interaction of the two sets of structures, and to attempt to arrive at some conclusion as to how far they are dependent upon, or independent of, one another.

While there is no reason to believe that the activity of the nervous system cannot go on apart from the action of internal secretions, there is no doubt that these have a material effect upon many nervous responses. This is strikingly exemplified by the influence of hyper- and hypothyroidism on the reflex responses of the central nervous system. It is also shown by the activation of the vagus terminations in the heart by iodothyrin and iodothyreoglobulin, by the facilitation in the action of the hypogastric nerves on the uterus by hypophysin, and by the action of adrenalin upon the neuro-cellular junction of the true sympathetic system. Even that purest example of nervous action—the stimulation of skeletal muscle by a motor nerve—is modified by the presence of the products of muscular activity—by chemical products which resemble in their nature the more typical internal secretions.

The Influence of the Nervous System on the Endocrinous Glands. That the nervous system influences the output of adrenalin and probably of iodothyreoglobulin has already been indicated (pp. 55 and 86). How far it may modify the production of other internal secretions is not known. But, while the functional activity of grafts indicates that the production of the secretions is not entirely dependent upon nerve impulses, it is very possible that future research will show that the production of many secretions is controlled by the nervous system.

The Influence of the Internal Secretions on the Nervous System. Evidence has already been adduced to show that some of the internal secretions act through the nervous system.

As regards **adrenalin** this evidence is conclusive. It is through the terminations of the true sympathetic system that all its effects are produced. Whether it directly stimulates these, or whether it simply sensitises them to the influence of the sympathetic nerves, is not at present decided, but the evidence seems to point to the second hypothesis (p. 57).

The very conclusive character of the evidence that adrenalin acts through the terminations of the true sympathetic system, renders it probable that its action upon metabolism is due to its influence upon the nerve terminations of the liver. Cavazzani long ago showed that stimulation of the splanchnic nerve to the liver increases glycogenolysis, and the more recent work of M'Leod shows that stimulation of the hepatic plexus leads to this only when the adrenals are intact.

The fact that adrenalin produces its effect after section of the splanchnic nerves indicates that its action is peripheral, and the antagonistic action of ergotoxin and adrenalin in the production of glycosuria, described by Miculicich, supports the view that in the liver, as elsewhere, the action is on nerve endings.

Hypophysin, as shown by Dale, acts at a point peripheral to that acted upon by adrenalin, since its activity is not modified by ergotoxin. But this does not prove that its action is upon the contractile substance of muscle fibre, for, as Langley has shown, the neuro-muscular junction is a more complicated structure than was at one time supposed. Further, the difference of its action on the arterioles of the bird and of the mammal, the difference of its action on the pregnant or recently pregnant and on the virgin uterus, and the peculiarity of its action on the renal as contrasted with the other arteries of the body (p. 67), all indicate that it acts upon something outside the contractile substance, upon something more nearly allied to the nerve endings. The only evidence which seems to tell markedly against this view, and which seems to indicate that pituitary may act upon muscle apart from nerve, is my observation of its augmentor action on the ventricles of the heart of the bird from which augmentor nerves are absent (p. 45). But the absence of the influence of extrinsic augmentor nerves does not disprove the existence of a local nervous mechanism.

The close similarity of the action of hypophysin to that of adrenalin upon carbohydrate metabolism (p. 68) suggests that it too acts upon the neuro-cellular junctions in the liver. But upon this point no direct experimental work has been done.

The action of the products of the thyroid gland upon the nervous system is well established. Its influence upon the brain and cord is shown by the marked differences in the condition of the activity of these structures in hypo- and in hyperthyroidism. Nothing could be more marked than the contrast between the response to stimuli in a case of Graves' disease and in a case of myxœdema. That the central synapses are influenced, no one can doubt.

The effect of thyroid removal upon the mobilisation of sugar (p. 79), and upon the action of adrenalin upon this mobilisation, indicates that both structures act upon the same mechanism, and that therefore, in all probability, the thyroid secretion produces its effect upon glycogenesis by stimulating the terminations of the true sympathetic in the liver.

Similar evidence is afforded by the results of Asher and von Rodt upon the activation of the splanchnic terminations by thyroid extracts (p. 83). Loewi's observation that adrenalin in the conjunctival sac produces its mydriatic effect in the hyperthyroidism of Graves' disease also indicates an action upon these terminations in the iris.

Further, the evidence adduced by von Cyon and by Asher and von Rodt indicates that thyroid secretion also acts upon the inhibitory vagal terminations and upon the depressor reflex mechanism.

Direct evidence as regards its mode of action on protein metabolism is wanting; but the indications that the influence upon the carbohydrate metabolism is through the peripheral nervous mechanism of the liver, renders it probable that the action upon proteins is at the same site. For the close association of protein catabolism with the formation of sugar is now recognised, and the relationship of the liver to the process is undoubted. The interesting observation by Mansfeld (p. 79), that the increased excretion of nitrogen which usually follows deprivation of oxygen does not occur after thyroidectomy, shows how close the association of the thyroid is with protein catabolism. It would almost seem as if its influence on the liver was necessary to enable that organ to respond to the acidosis of mal-oxygenation in order to catabolise the disintegrated protein for excretion. As already stated, Mansfeld takes another view of the mode of production of the effect, a view which hardly seems to explain the facts of the case.

While the features of hyperthyroidism point so clearly to the implication of the nervous system, the disturbances in growth in hypothyroidism, as exemplified in cretinism and myxœdema, suggest the possibility of an action apart from nerve. The stunted growth with the associated bone changes and the low temperature might be due to a generalised action upon the tissues. But the evidence already adduced (p. 18) of the influence of the nervous system upon the development and nutrition even of such tissues as bone shows that these effects may be produced through an action upon nerve, possibly of the nature of a vaso-motor reflex (Fig. 7).

The close correspondence of the thyroid and of the true **pituitary** as regards their origin, and as regards their mode of action on the metabolism, renders it probable that they produce their effects by operating through a common structure. But no observations are at present forthcoming as to how the pituitary acts.

The internal secretion of the **pancreas** has been shown to check the mobilisation of sugar which is facilitated by adrenalin, and less markedly perhaps, by products of the thyroid. The evidence that these latter act upon the terminations of the true sympathetic to produce their effect has been already considered, and it seems probable that the secretion of the pancreas acts upon the same structures in the opposite direction, inhibiting their activity (Fig. 5).

The observations of Loewi, that, in the diabetes which follows excision of the pancreas, the action of adrenalin on the pupil is increased, suggests the probability that this inhibitory action of the pancreas extends beyond the liver to other sympathetic terminations.

The action of **secretin** on the pancreas was assumed by Bayliss and Starling to be a direct one on the cells, because it occurred after the administration of atropine. But the more recent work of Cushney tends to show that the blocking action of atropine does not apply to every stimulus acting upon the nerve. On the uterus it does not interfere with the effect of stimulation of the hypogastric nerve or with the action of adrenalin, while it antagonises pilocarpine. The work of Magnus on the gut also shows that it is not safe to conclude that the action of the nervous mechanism is excluded by atropine. A study of the influence of nicotine on the action of secretin might yield valuable results.

The **parathyroids** and **thymus** have been already linked together on account of the similarity of their origin and on account of certain correspondence in their physiological actions. The results of many investigators on the parathyroids, and of Basch and Klose and Vogt on the thymus, show that removal is followed by instability of the central nervous system (pp. 125 and 114). Both seem to exercise a depressing or regulating effect on the spinal synapses, an action opposite to that of the thyroid. The question of whether this is primary, or whether it is not the result of metabolic changes, has been already discussed, and reasons have been given for rejecting alike the theory of the decrease in the calcium of the tissues and of the increase of ammonia in the blood as factors in the production of the symptoms of parathyroidectomy. The probability of an acid intoxication being the causal factor has also been considered, and the absence of evidence has been indicated (p. 131).

In the present state of our knowledge, there is no more reason to consider that the metabolic disturbances, which follow removal of the parathyroids, are primary and causal to the nervous symptoms, than to suppose that the nervous symptoms following thyroidectomy are caused by the metabolic disturbances. In both, the action of the product of the gland is probably a direct one upon the metabolism of the nervous system and of the body generally.

Our knowledge as to the mode of action of the **thymus** is admittedly imperfect. No evidence is forthcoming as to how it produces its reciprocal effect with the testes upon growth. As already indicated, the nervous symptoms recorded by Klose and Vogt point to its having a similar effect upon the reflex spinal mechanism as has the parathyroid.

In the **gonads** two distinct sets of actions have to be considered: first, their action in producing the phenomena of sexual life, and, second, their action on growth and development.

As regards the former there is, of course, no doubt that it is through the nervous system. This is well illustrated throughout the animal kingdom. In birds the activity of the gonads determine not only the assumption of the breeding plumage, but also the development of song and of the wonderful nidifying reflexes. It activates the nervous system to a whole series of fresh responses. In every other group of vertebrates the same phenomena are manifest. A most striking example is seen in the clasping reflex of the male frog in the breeding season. This is a reflex which can be elicited only at this season by touching the skin over the sternum, and it can be elicited even when the head and the lower part of the body have been removed. On the other hand, at the breeding season MacLean has recorded that the inhibition of the heart by stimulation of the vagus is not readily produced, the nervous mechanism being modified by the state of the reproductive organs.

The evidence is by no means conclusive as regards the mode of action of the gonads upon growth and development. They, with their abundant interstitial cells, along with the closely allied inter-renal structures and the early thymus are all developed while as yet the nervous system is in a rudimentary condition, and while the regulating influence of hereditary inertia is the dominant controlling mechanism. So far, evidence is wanting to show that their effect is produced through the nervous system, although it is possible that they exert their influence by acting through the vaso-motor mechanism by which the blood supply of the tissues is controlled (Fig. 7).

It would almost seem as if two sets of chemical regulators exist, one which might be called the **Primary Chemical Regulators**, possibly acting directly upon the metabolism of the tissues as modifiers of hereditary inertia. These are the gonads in embryonic life, and possibly the inter-renal system and the thymus. The other set might be called the **Neuro-Chemical Regulators**, since they act through the nervous system. These would include the chromaffin system, the hypophysis, the thyroid, the pancreas, and the parathyroids. Evidence points to the thymus and gonads as also acting in this way in post-fœtal life.

The part played by each of the great regulators of metabolism throughout the course of embryonic and post-embryonic life might be represented diagrammatically as shown in Fig. 8.

In early embryonic life the force of hereditary inertia is the dominating factor. Later, the chemical regulation of the gonads, inter-renals and thymus come into play as modifying factors. Still later, the influence of the nervous system becomes more and more prominent, and finally this influence of the nervous system is further directed and controlled by the production of internal secretions from such structures as the chromaffin tissue and the other neuro-chemical regulators.

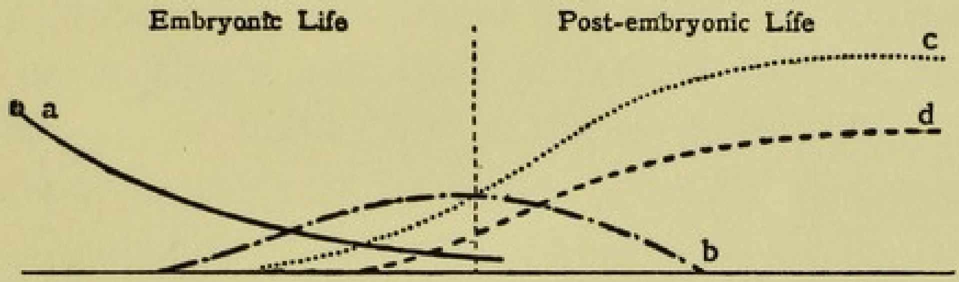


FIG. 8.—To show the relative parts played during embryonic and post-embryonic life in the regulation of metabolism by (*a*) hereditary inertia; (*b*) the primary chemical regulators; (*c*) the nervous system, and (*d*) the neuro-chemical regulators.

This survey of the interrelationship of the internal secretions and the nervous system seems to indicate a dominance of the latter by the former. The mode of action of the nervous system at any time is largely controlled by the activity of the various secretions, although their amount is in some measure influenced by the action of the nervous system, either as the result of external conditions or, possibly, by the precedent activity of other internal secretions. If this is so, the question arises how far, not only the bodily development and configuration, but also the mental development and character of the individual are simply a matter of the condition of the endocrinous structures, and how far, in abnormal childhood, education may come to be supplemented by some attempt to regulate the supply of defective secretions.

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SECTION VI.

THE EVOLUTION OF THE ENDOCRINOUS GLANDS.

It is impossible to leave the study of the endocrinous glands and their secretions without some attempt to solve the problem—How did they originate, and how were their functions developed?

Comparative anatomy throws little light upon these questions, for, so far, no homologues of these structures have been discovered in invertebrates. It is true that a study of the comparative anatomy of the supra-renal glands has shown very clearly the independence of the adrenal or medullary part and the inter-renal or cortical part.

At one time the view was much in vogue that these various structures had for their purpose the de-toxication of various hypothetical products of metabolism. This view was long held as regards the suprarenals, and Luciani supports it as regards the thyroid, even at the present time. The evidence in its favour has never been strong, and the study of the action of extracts of the various glands has completely refuted it. It is still maintained by some in explanation of the action of the parathyroids. But it is inconceivable that such minute pieces of tissue, as Halstead has shown are sufficient to obviate the onset of symptoms, can act in such a manner.

The theory supported by von Cyon that the thyroid and pituitary, along with the supra-renals, are an arrangement for the adjustment of the vascular system, and more especially of the intra-cranial circulation, is ingeniously supported by its author in his book, *Die Gefässdrüse.*

But the facts adduced, when read alongside of other evidence, do not seem to me to support the view.

These two theories do not require further examination, and some other explanation of the origin of the endocrinous glands must be sought for.

The source and the position of some of the glands seem to be of significance. The thymus and parathyroids develop from the branchial arches along which the arterial blood flows to the body in the embryo of all vertebrates and throughout life in fishes.

This suggests that such structures may have a regulating action on the supply of certain materials to the tissues, just as the liver, placed between the gut and the tissues, regulates the supply of sugar to the latter. The thyroid, too, lies in close proximity to the aorta and its branches, and its action might thus be of the same kind.

It is not necessary to assume that a mere retaining and dispensing of the materials is the only action of the structures. Just as the liver may elaborate its sugar from other substances than the carbohydrates, so these structures may produce profound changes in the materials taken from the blood.

What is the nature of the substances? The chemistry of only two—iodothyreoglobulin and adrenalin—is known to us. But the constitution of these two bodies affords a hint as to the probable character of the other substances. The iodine compound of the thyroid is accumulated in the colloid from iodine in the food or from iodine administered in various forms. It is a definite organic compound, which has a physiological action very different from that of the iodine preparations.

Adrenalin is allied to tyrosin and to the group of derivatives of the protein molecule, which contain the benzene nucleus. It is probably built up by a process of syntheses in the chromaffin tissue. The presence of a minute quantity of each of these in the blood is essential for the proper action of certain of the tissues, and the absence of each is followed by characteristic alterations in the metabolism.

These facts suggest very strongly that, in the action of these substances, we have something analogous to the influence of minute traces of inorganic salts, which was first demonstrated by Ringer. Small as is the amount of these, their presence, even in such small amounts, is absolutely essential for the maintenance of the activities of the various tissues, and not only is the absolute amount of each of importance, but the relative proportions in which they occur is of equal moment. And so it is with the internal secretions. A certain minimum amount of each seems to be essential, and some proportion between the amounts of each must be maintained if the metabolism is to continue in its normal course.

The importance of such minimal amounts of certain of the constituents of the proteins of the food has been more recently emphasised by Willcock and Hopkins in their work upon feeding with zein, a protein in which tyrosin and tryptophane are absent. They found that mice fed upon this along with carbohydrates and fats lost weight and died in a short time, but that, when tryptophane was added, life was markedly prolonged, although weight was not gained. They conclude that the tryptophane must yield material for the formation of something essential to the metabolism, and they compare this with the elaboration of adrenalin.

The evidence we possess thus seems to indicate that iodothyreoglobulin and adrenalin belong to this group of substances. At present we are completely in the dark as to the nature of the other internal secretions, but the essential similarity in the kind of results which are produced by the removal of the structures yielding them strongly suggests that their mode of action is of the same kind.

Thus sugar cannot be properly stored in the absence of the internal secretion of the pancreas, while in the absence of the secretions of the chromaffin tissue, of the hypophysis and of the thyroid it is imperfectly mobilised. For the proper growth of bone and for the development of the special sexual characters, small amounts of gonadin are necessary. Without the parathyroids the stability of the spinal synapses is no longer maintained, while, on the other hand, for the normal responsiveness of these synapses the secretion of the thyroid is necessary. The fact that more than one of these organs may act in a similar manner allows of compensation being established after removal of one—as is seen in the case of the thymus and gonads.

It seems to me that such a conception is more in accordance with the facts which we possess than that of a series of hormones or excitors directly calling forth the activity of the various tissues.

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