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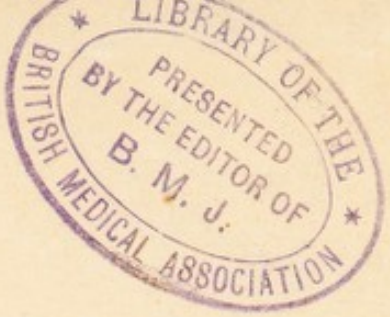
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FEVER, HEAT REGULATION, CLIMATE, AND THE THYROID-ADRENAL APPARATUS

BY

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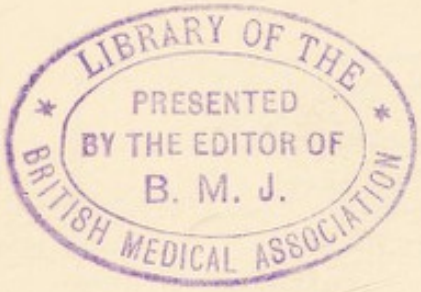

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CHAPTER I

INTRODUCTION

THE conclusions reached in this treatise can be stated in a few words and may be summarised at the beginning so as to make it easier for the reader to follow the argument.

With the exception of respiration, all the factors concerned in the heat regulation of warm-blooded animals are under the direct control of the sympathetic nervous system, and therefore subject to control by the functional activity of the thyroid and adrenal glands. Increased functional activity of these glands has the effect of stimulating the sympathetic. There is therefore both a nervous and a humoral apparatus for heat regulation. Stimulation of the sympathetic increases metabolism and thereby increases heat production. While it diminishes heat loss through constriction of the cutaneous blood-vessels it increases heat loss through stimulation of the sweat glands. This latter effect may be inhibited by the constriction of the cutaneous blood-vessels. In furry animals which cannot regulate heat loss by sweating this function is taken over by the arrectores pilorum: in these animals sympathetic stimulation increases heat loss through stimulation of the arrectores pilorum. This mechanism is, however, less efficient than that of the sweat glands. It follows, therefore, that stimulation of the sympathetic by increasing heat production and by preventing a compensating increase in the heat loss or actually diminishing it produces a type of fever: "sympathetic fever". Such a fever can be induced by increased functional activity of the thyroid and adrenal glands, even without the presence of bacteria. Evidence is adduced

that in many of the fevers due to bacterial infections there is an increased functional activity of these glands. In fever there is a change in body temperature, or as it may be called, the "internal thermal environment", due to the stimulation of the thyroid and adrenal glands. Conversely the functional activity of these glands can be brought into play by changing the "external thermal environment". Exposure to cold, which calls for increased heat production and diminished heat loss, stimulates these glands to increased activity. Exposure to heat diminishes their activity. The thyroid and adrenal glands represent, therefore, a humoral apparatus for the heat regulation of the body. This accounts for the physiological and psychological effects of climate. A bracing climate is one which stimulates the sympathetic and the thyroid and adrenal glands, a "relaxing" climate one which fails to stimulate them. The work of Leonard Hill and Argyle Campbell has shown that one of the effects of a bracing climatic environment, such as open-air treatment for instance, is a rise in metabolism. But a rise in metabolism in itself does not account for the beneficial effects of such an environment. The explanation is to be found in the increased functional activity of the thyroid-adrenal apparatus of which the rise in metabolism is one manifestation.

The conception of heat regulation as a function of the sympathetic, which emerges from these conclusions, enables us to dispense with the idea of a heat centre or of several centres, which are supposed to function like a thermostat and which in fever are supposed to be "set" at a higher temperature. It is curious that such a crudely vitalistic conception, which really explains nothing, should have dominated physiological and pathological thought for such a long time. Since heat regulation is a function of the sympathetic, the so-called heat centre in the tuber cinereum is explicable as a group of nerve-cells representing the central connexions of the sympathetic.

Of even greater general significance is the fact that changes in the external thermal environment affect the

activity and structure of organs like the thyroid and adrenal glands which have such a profound influence on the physical and mental make-up of the organism. This fact affords a physiological basis for the study of the fascinating problem of the influence of climate on man, which is dealt with in the last chapter. The important work of Professor Ellsworth Huntington, which furnishes the meteorological and geographical data, only came to our notice accidentally after this treatise had been almost completed. It was therefore all the more striking to find how completely the physiological conception fitted in with his deductions based on physical data.

It has been suggested repeatedly that the endocrine organs play an important part in the evolution of species and of the human species in particular, while climate has always been recognised as an important evolutionary factor. Here, also, the observations recorded in this treatise offer a physiological basis. It is known that these glands affect profoundly not only the mental but also the physical make-up of the organism, such as, for instance, pigmentation, growth of hair. We find now that these glands are themselves affected by such environmental factors as climate. These glands represent, therefore, a communicating link by which the outer world of an organism is capable of influencing its inner world. In view of the importance of this point it is gratifying to note that the stimulation of adrenal activity by cold, which was demonstrated in 1918 by the histochemical method, has been confirmed during the last few years by different experimental methods. Hartman used the denervated iris as the test object, while Cannon studied the increase in blood sugar resulting from exposure to cold in the presence and absence of the adrenals. These methods are, however, indirect methods. A large amount of controversial writing has accumulated concerning the correct interpretation of the results obtained by such indirect methods in the study of other functions of the adrenal

gland, because the results are often capable of different interpretations. The faulty nature of most of the arguments based on such methods has been forcibly summarised by G. W. Stewart. The use of such indirect methods in the study of the relation of the thyroid gland to heat regulation—experiments which will be discussed presently—has led to erroneous conclusions as, for instance, in the work of Mansfeld who holds that the thyroid secretes a hormone which inhibits metabolism. The histochemical method which led to the recognition of cold as a stimulus to the adrenal is a direct method, to which these criticisms do not apply. The principle of the method is the same as that by which one investigates the secretion of glands with ducts, such as the pancreas or the salivary glands, where the secretion can be seen with the naked eye flowing out of the duct, when the glands are secreting. Our knowledge concerning the factors determining the secretory activity of the pancreas would have remained very fragmentary and uncertain if we had to rely on the indirect evidence of increased or diminished digestion of the contents of the alimentary tract. In studying the functional activity of endocrine organs one cannot for obvious reasons see with the naked eye the pouring out of their specific secretion. Their internal secretion has to be rendered visible so that, in order to find out when they are resting and when they are secreting, a direct appeal can be made to the cells rather than to the organ as a whole. The same criticism applies to the use of quantitative chemical estimations of the specific hormones—adrenalin, for instance—or of the cortical lipoid of the adrenal. Though these methods are quantitatively accurate they give no direct information on the functional activity of the gland to which they are applied. That becomes a matter of interpretation, in which the chemical accuracy is no guarantee of the accuracy of the physiological reasoning. In fact, in most cases the conclusions drawn from such estimations have been erroneous. These

methods, moreover, give no indication of the distribution of the estimated substances in the organ—a factor which, as revealed by histological methods, is of considerable importance in understanding the functional mechanism of the adrenal gland.

The difficulty of correctly interpreting the results obtained by the indirect method has led some writers to take up an extreme critical position and to deny to the adrenal medulla a process of internal secretion and to attribute this function entirely to the cortex. The evidence afforded by the direct method and presented in the following pages has disposed of this somewhat hypercritical view as well as of the idea that the medulla of the mammalian adrenal is functionally an organ independent of the cortex. Instead, the method discloses a mutual interaction of cortex and medulla, allowing of the development of an extremely delicate mechanism of self-control and inhibition on the one hand and of a rapid adaptation to an increased functional demand on the other.

No other method could have given as deep an insight into this intricate interrelationship. The elaboration of similar methods for the other endocrine organs which would enable us to see what is actually happening in the cells of these organs in various conditions should solve many of the intricate problems of endocrinology. There are indications that the islets of Langerhans and probably also the pituitary are involved in the heat regulation of the body, either directly or indirectly. That they are not dealt with in the following pages is merely due to the fact that the evidence on this point is as yet not sufficiently precise.

There is one consideration which has come out as being of special importance in the technique of investigating the thyroid-adrenal apparatus, namely, the necessity of avoiding as much as possible the use of anæsthetics. One has only to glance at Plate 11 showing the changes induced in the adrenal gland by an anæsthetic in order to

realise what a disturbing factor is introduced by its use. This disturbing influence manifests itself in many ways. For instance, ether anæsthesia greatly depresses the vaso-motor response to adrenalin (Berry), and as stated more fully in the text it also depresses the respiratory response and the reaction to pyrogenic substances. Whether the same holds good for the thyroid has not yet been made out. But, at any rate, it is necessary to realise that the conditions presented by an anæsthetised animal may be very different from normal physiological conditions. It is of special importance to exclude the fallacies introduced by anæsthesia when one wishes to investigate the heat regulation of the body, since this mechanism is partly put out of action by anæsthetics as evidenced by the fall of temperature produced by anæsthesia.

The conception outlined at the outset and the experimental basis on which it rests have been published in a number of papers of which a list is appended to this section so as to avoid repeated references in the text. These papers are to be considered of the nature of progress reports and contain evidence collected in attempting to test the views submitted in this volume from every possible angle. Since the publication of our first papers on this subject a considerable amount of confirmatory evidence has been adduced by other workers, especially in America. So far as I am aware nothing has been published which would question the correctness of our views. With the exception of Chapters VII. and VIII., which have appeared quite recently as separate papers and have merely been brought up to date, the present treatise has been completely rewritten and is not merely a collection of reprints or a repetition of work already published. In the following pages an attempt is made to present the subject as a consecutive argument in support of which a good deal of unpublished material is adduced. In order to keep the argument as much as possible to the point certain

aspects of the problems which have been discussed fully in published papers, such as the effect of the thyroid hormone on metabolism or the physiology of heatstroke, are dealt with as briefly as possible. For the same reason a general discussion of the vast literature on closely related problems, such as the interrelationship of various endocrine organs, has been avoided, since the excellent text-books of Schäfer, of Swale Vincent, of Biedl and of Schilf are available for that purpose.

It will be convenient to refer here briefly to the general aspects of the literature on the subject while reserving the discussion of special points to the special chapters. So far as the suprarenal glands are concerned our observations published in 1916 and extended in 1918 and 1919 were the first to establish conclusively a relationship between these glands and heat regulation by showing that exposure to cold is a powerful stimulus to their functional activity. The later work of Boothby and Sandiford, Aub, Hartman, Cannon and others has confirmed this conception by a great number of experiments planned along different lines. The defective heat regulation of patients suffering from myxœdema directed at an early stage the attention of workers to the reaction of thyroidectomised animals to changes in temperature (Horsley, von Eiselsberg, Lorrain Smith). At that time the distinction between the thyroid and parathyroid glands was not understood. Many of the earlier observations are therefore vitiated by the fact that the parathyroids had been removed together with the thyroid gland and that the animals were suffering more from the absence of the parathyroids than from the absence of the thyroid alone. There was, however, a general agreement that such animals are less able to resist a cold environment and this has been confirmed by the recent work of Schenk, of Cori and of Korenchevsky. But the statements concerning their reaction to a hot environment are very contradictory. Even the later work of Boldyreff, in 1913, which

was made on animals in which both thyroids and parathyroids had been removed, suffered from the same fallacy. He found, for instance, that his thyroidectomised animals reacted to heating more readily by a rise in temperature than normal animals and developed tetanic convulsions. If these observations were correct it would be difficult to formulate a rational conception for the function of the thyroid in the heat regulation of the body. But it is clear from our present knowledge of the function of the parathyroids and from the more recent work on the thyroid gland that many of the results observed were due to the absence of the parathyroids and throw no light on the relation of the thyroid to heat regulation. Another line of investigation was followed by Loewy and by Mansfeld. Mansfeld had found, in 1913, in rabbits that the perfused heart removed after heat piqure consumed more sugar than the heart of a normal animal. Loewy (1914) confirmed this finding and showed further that the heart of thyroidectomised animals did not show this increased consumption of glucose after heat piqure. Mansfeld (1915) also found that the increased nitrogen excretion in the fever produced by the injection of bacteria into normal animals failed to appear in thyroidectomised animals. In 1920 Mansfeld published another paper showing that the glucose consumption of the perfused heart depended on the thermal environment of the animals previous to the removal of the heart ; the heart of cooled animals consumed two to three times more glucose than that of animals kept in a warm environment of about 25° C. Moreover, the serum of cooled animals, when added to the perfusion-fluid of the heart taken from overheated animals, greatly increased the sugar consumption. Conversely the serum of overheated animals when added to the perfusion-fluid of the heart taken from a cooled animal greatly reduced its initial high glucose consumption. In thyroidectomised animals subjected to cooling and overheating the serum failed to acquire the stimulat-

ing and inhibiting effects on the glucose consumption of another heart preparation.

If these results are accepted one must conclude with Mansfeld that the chemical heat regulation is dependent entirely on the hormones of the thyroid and that this gland secretes two hormones, one which stimulates and another which inhibits metabolism. This view is open to the following objections. Thyroidectomised animals still maintain their temperature and, as our observations detailed in Chapter IV. show, are still capable of reacting with fever to either injection of β-tetrahydronaphthylamine or bacterial infections. The same is true for the fever produced by heat piqure, as Asher and his collaborators found. Both our observations and those of Asher and his collaborators show that thyroidectomised animals differ from normal animals only in so far as they react to these pyrogenic agents more sluggishly. Their heat-regulating mechanism is impaired but not abolished. This is confirmed by the more recent work of Cori, of Schenk and of Korenchevsky. Another objection arises from our observations that the adrenal glands are as much concerned in the heat regulation of the body as the thyroid. There is no evidence, so far as I am aware, that the addition of thyroid extracts to the perfusion-fluid of a heart preparation increases its sugar consumption. It is curious that this crucial experiment has not been carried out by Mansfeld. We know, on the other hand, from the work of Patterson and Starling and of Evans, that the addition of adrenalin produces a marked increase in the glucose consumption and in the gaseous metabolism of the perfused heart which is accompanied by an acceleration of the heart beat. The observations of Mansfeld give no information on the rate of the perfused heart. The second suggestion that the thyroid secretes a hormone which inhibits metabolism is contrary to all known facts concerning the effects of the thyroid hormone on metabolism. There is not even any evidence that any

of the other known hormones are able to produce such an effect. If the actual results of Mansfeld can be confirmed they raise doubts whether such indirect evidence, which is always capable of other interpretations, can form a sufficiently reliable basis for the conclusions he has drawn from them.

We have dealt with these observations in some detail because they offer a striking illustration of our contention that indirect evidence does not present a reliable basis for the study of the activity of the endocrine organs. Direct and conclusive evidence on the relation of the thyroid gland to heat regulation can be obtained by a study of the gland itself under conditions involving activity of the heat-regulating mechanism. The results are then quite unequivocal. Conditions involving increased heat production, such as a change from a hot to a cold environment or the sympathetic fever induced by the injection of pyrogenic substance, produces an intense secretory activity of the thyroid, of which the disappearance of colloid is the most obvious feature. Conversely change from a cold to a hot environment which reduces heat production is accompanied by an accumulation of colloid and by cytological changes in the cells of the gland indicating diminished cellular activity. The disappearance of colloid in cold and its accumulation on exposure to heat have been confirmed by Mills and by Hart.

Additional evidence is furnished by the observations already referred to that thyroid feeding itself increases the heat production, raises the temperature and renders an animal more susceptible to the action of pyrogenic substances, while in the absence of the thyroid all these effects are reversed.

It is impossible to understand the relation of the adrenal and thyroid glands to the chemical heat regulation, *i.e.* the mechanism by which heat production can be increased, without a comprehension of the glycogenic function of the liver. For half a century the true nature

of this function, which was so clearly recognised by Claude Bernard, has been completely misunderstood and is still being misconceived in current physiological literature. A special chapter (Chapter VI.) is therefore devoted to this subject, and it is shown that the liver by virtue of the glycogenic function is the central organ of metabolism much in the same way as the heart is the central organ of circulation. The only confirmation of our view which has appeared so far is a paper from Macleod's laboratory by Marcovicz.

If, as we maintain, the thyroid-adrenal apparatus is concerned in the heat regulation of the body, it is obvious there must be pathological evidence in support of this view. This is presented in Chapter VIII., in which it is shown that lesions of these glands are frequently accompanied by disturbances of heat regulation and conversely that disturbances of heat regulation, such as fever, frequently produce lesions in these glands. In discussing the evidence based on pathological material I have relied not only on the evidence recorded in the literature but also on material collected from University College Hospital, St. Mary's Hospital and from the Hospital for Sick Children in Great Ormond Street. It is a pleasant duty to thank Dr. Th. W. P. Lawrence, Sir Bernard Spilsbury, Prof. E. H. Kettle and Dr. Donald Paterson for the generous facilities which they have afforded me.

An investigation into the thyroid-adrenal apparatus, fever and heat regulation does not seem to have any obvious relation to the investigation of cancer. As a matter of fact, however, it had its origin in an investigation begun fourteen years ago on the influence of various hormones, and of the thyroid hormone in particular, on the growth of cancer. It seemed of considerable interest not only from the therapeutic but also from the general theoretical point of view to determine whether or not cancer cells were subject to the influence of a hormone such as that of the thyroid gland which so profoundly

affects the whole metabolism of the normal organism. It was soon realised, however, that the relations of these glands to metabolism were at the time so imperfectly understood that, in order to avoid sheer empiricism, it was necessary to establish a more satisfactory physiological basis for the investigation.

A second line of investigation, which at first seemed in no way related to the study of endocrine organs, had its inception in the observation that the few authenticated cases in which a spontaneous cure of cancer had occurred in the human subject had almost always associated with the beginning regression of the growth a bacterial infection accompanied by a pyrexia. For this regression the bacterial toxins have generally been held to have been responsible, and the use of "Coley's fluid" as a therapeutic measure has been the practical therapeutic application of this idea. It seemed possible, however, that the regression of cancerous growths, when it occurred, was due not to the toxins but to the condition of fever which had existed in these cases. This led to an investigation of the mechanism of fever. How these two lines of investigations converged the following pages will show.

This book may therefore be offered as a by-product of cancer research. It is a pleasure to acknowledge my indebtedness to Dr. J. A. Murray for his unfailing encouragement, advice and criticism, and to Dr. R. J. Ludford for his assistance in reading the proofs and for his pictographic summary of the changes occurring in the thyroid and adrenal glands in the different phases of their functional activity.

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CHAPTER II

THE HISTOCHEMICAL METHOD—THE ADRENAL MEDULLA AT REST

THE histochemical method which has been used as the basis of our investigations of the functional activity of the adrenal glands is one which has not hitherto been applied to the investigation of endocrine organs, although it has been a recognised method in the physiological examination of externally secreting glands, such as the pancreas and salivary glands. It consists in rendering visible the specific secretory granules of adrenalin in the cells of the adrenal medulla and observing their secretion into the blood when suitable stimuli are applied. The need for such a method was felt because during the last twenty years the functional activity of the adrenal medulla has been the centre of a prolonged controversy. With an endocrine organ the act of secretion is not rendered visible to the naked eye like that of an externally secreting gland by a flowing out of the secretion through a duct. The ordinary physiological methods of investigation to demonstrate the actual occurrence of an internal secretion depend, therefore, on indirect methods involving a highly complicated technique, the results of which are often capable of different interpretations. They also involve, as a rule, the application of anæsthetics which are a disturbing factor because they themselves profoundly affect both the functional activity of the adrenal medulla and the mode of action of adrenalin. As a result there is at present, in spite of the extensive

work of the most highly skilled experimentalists, very little agreement as to the conditions under which the adrenal medulla is functionally active. In fact, some authorities have denied that adrenalin is ever secreted by the adrenal medulla in amounts sufficient to produce its physiological effects, and the physiological importance of the adrenal medulla has been belittled at the expense of the adrenal cortex.

The histochemical method has the advantage of giving direct and conclusive evidence, in a normal organism and without the disturbing intervention of anæsthetics, of the actual process of secretion of adrenalin from the medulla into the blood-stream, when the organism is subjected to experimental variations. The method has its limitations. It is not quantitative. For reasons which will become apparent presently the method is particularly applicable to very small adrenal glands, such as the adrenal of the mouse, which can be used in their entirety.

The principle of the histochemical method consists in rendering the granules of adrenalin visible by fixing the gland in the vapour of osmic acid. The use of osmic vapour is based on two considerations. Adrenalin is easily oxidised and therefore readily reduces osmic acid to the black lower oxides or, perhaps, even to the metal itself. The use of the vapour instead of the watery solution is necessary because adrenalin is so readily soluble, that the use of any fluid fixative will dissolve the granules of adrenalin before it can fix them in their normal position in the cytoplasm of the cell. Even the bichromate solutions which have hitherto been considered to be specific fixatives of cells containing adrenalin fail to give any evidence of granules of adrenalin in the cytoplasm or indeed of other cytological details or of the process of secretion of adrenalin, but only give a brown lake filling the whole cell homogeneously.

In order to obtain satisfactory results with the osmic vapour method it is necessary to observe the following

details. The glands must be fresh. They are removed from the animal without squeezing the gland between the forceps. The adipose tissue which surrounds the adrenals in a mouse very closely is removed carefully and as completely as possible with a sharp narrow-bladed knife. The gland is then ready for fixation. The simplest and most efficient arrangement for that purpose consists of a small glass-stoppered weighing bottle, 4 cm. high and with a diameter of 2 cm., having a capacity of about 8 c.c. About 2-3 c.c. of 2 per cent osmic acid solution are placed in these weighing bottles. The adrenal rests on a piece of gauze stretched over a piece of wide glass tubing about ½ cm. in diameter and about 2½ cm. high, which is placed into the weighing bottle. After firmly inserting the glass stopper, the weighing bottle is placed in an incubator which must be kept at such a temperature that the fluid within the weighing bottles is heated rapidly to a temperature of 37° C. We have used for that purpose an oven for embedding in paraffin. When a small piece of tissue is used, such as a mouse's adrenal, the weighing bottle is left in the incubator for one and a quarter hours. The adrenal is then removed and placed in repeatedly changed 60 per cent alcohol for about twenty hours. It is brought through the ascending series of alcohols into xylol, embedded in paraffin, and cut in serial sections of 5-7 μ thickness. In order to examine the sections it is only necessary to remove the paraffin with xylol and mount in Canada balsam or damar. The sections show then the cortical cells filled with black globules of lipoids and the medullary cells filled with the much finer black granules of adrenalin. It is possible to differentiate between these two groups of substances by immersing the sections for twenty to thirty minutes in crude turpentine after having previously removed the paraffin with xylol. When the turpentine is again washed off with xylol and the sections mounted in balsam, all the lipoid globules have been

removed, so that the cortical cells show up now as a ring of highly vacuolated cells surrounding the intensely black medulla, which has not been affected by the turpentine. The preparations are permanent for a few years so far as the staining of the adrenalin granules in the medulla is concerned, which fades only very slowly. The lipoid globules of the cortex, however, become rapidly dissolved by the balsam, even if no treatment with turpentine has been applied previously.

When slightly larger glands are to be examined, such as the adrenals of the rat, it is best to halve the gland with a sharp razor and to fix the two halves in osmic vapour for one and a half hours. For the examination of the relatively large glands of guinea-pigs, rabbits, dogs, cats, etc., it is necessary to cut as thin a slice of the gland as possible with a razor and fix it in osmic vapour, varying the time from one and a half to two hours according to the thickness of the slice. The disadvantage of using these larger glands for experimental purposes is that the unavoidable handling of the gland may produce changes, and that only a small portion of the medulla can be subjected to examination. With the adrenal of the mouse handling can be avoided, and the gland is so small that the whole medulla can be displayed in serial sections in three large slides so as to give a complete picture of the state of functional activity throughout the whole medulla. Moreover, successful fixation is most readily and regularly obtained with the mouse's adrenal. In fact, after a few trials, there is no difficulty in obtaining completely successful results in practically every case if the details of the procedure given above are followed. The points demanding particular attention are : to make the removal of the adipose tissue surrounding the gland as complete as possible, and to use a suitable incubator which will rapidly raise the temperature of the contents of the weighing bottle to 37° C.

Material fixed in osmic vapour in this way can be

stained by the ordinary staining methods if the osmic stain is removed first from both cortex and medulla. This can be done readily by immersing the sections, after the paraffin has been removed, in 80 per cent alcohol containing 10 per cent of hydrogen peroxide of commercial strength. After about half an hour the section can be removed, passed through the descending series of alcohols into water and stained with Heidenhain's iron-hæmatoxylin: this gives good histological results with such material.

Fixation in solutions containing osmic acid—in other words, fixatives such as osmic acid solution, or Fleming—does not give the striking results obtained with the osmic vapour method because, as already stated, the water or other solvent of the fixative dissolves the granules of adrenalin before they can be fixed.

If the method is applied to the resting adrenal of a normal mouse the appearances presented in Plate 1 and Plate 2 are obtained. It should be clearly understood that these are drawn from sections which have not been subjected to any further staining. Plate 1 is a low-power view through the middle of the gland, where the medulla has attained its maximal width and length. The cortex from which, in this preparation, the lipoid globules have been removed by treatment with turpentine shows the typical arrangement in the three zones, of which the innermost one, the zona reticularis, appears as a very narrow vascular strip of cells sharply and evenly delineated from the medulla. This sharp division is sometimes absent in female animals. The lipoid globules occupy the outer part of the cortex, that is to say, the zona glomerulosa and the outer half of the zona fasciculata. The inner part of the cortex is in the resting gland free, or almost free, from lipoid. The medulla appears as an even sheet of cells arranged in groups of round alveoli. The capillary spaces which separate these alveoli are almost all closed in the resting gland, and only the large central vein, of

which part is represented in Plate 2, and its immediate tributaries remain patent. Two types of cells can be distinguished. One type is filled with exceedingly fine granules stained a dull black with osmic acid. With an oil-immersion lens the separate granules are clearly visible, but their fineness renders an adequate reproduction difficult, and it is necessary in looking at the figures to bear in mind that the cells are not filled with a homogeneous black material. The other type of cell has a clear, greyish, turgid appearance and contains one or more " globoid bodies " of varying size stained black with osmic acid. These globoid bodies may lie in close proximity to the nucleus or at the periphery of the cell or at any intermediate position in the cytoplasm, or they may be seen in the intercellular spaces. Each type of cell is arranged in groups, so that a whole alveolus is composed, as a rule, entirely either of the one or the other type. In a normal resting gland the black type of cell preponderates. The nuclei of both types of cells are large, clear and turgid. The possibility that these two types of cells represent two genetically different types cannot be excluded altogether. But since their relative proportions vary greatly in different individuals, it is more probable that they represent two different stages of functional activity. The black globoid bodies are not lipoid, since they do not stain with Sudan or Scharlach, show no double refraction in polarised light and are not removed by treatment with turpentine. Similar black bodies may appear in the cells of the zona reticularis but only when the gland is stimulated to activity. Plate 3 is taken from such a gland and represents a group of medullary cells in immediate proximity to the zona reticularis, in the cells of which two black globoid bodies which are not lipoid are present. These globoid bodies are either adrenalin or an immediate precursor of adrenalin. This point will be discussed again in greater detail in the next chapter.

When the osmic vapour method is applied to the

adrenal glands of other mammals the same reaction is obtained : the medullary cells are filled with a mass of fine dull black granules. The only difference is that in some species the islets of white turgid cells containing the black globoid bodies are either rare or completely absent. In order to test the validity of the osmic vapour method as a histochemical method for adrenalin-containing cells we have applied it to the adrenal glands of amphibians and of birds in which the adrenalin-containing cells are scattered throughout the cortical cells instead of forming a compact medulla as they do in mammals. In every case the adrenalin-containing cells are picked out as cells containing numerous fine black granules which are not decolorised or dissolved by turpentine. The only obvious difference, apart from the anatomical arrangement, is that the reaction is not nearly so intense in the frog as in the sparrow or the mouse ; the granules are not so densely packed, and on account of this the adrenalin-containing cells of the frog do not show up with the same intense blackness. The application of the method to other endocrine organs (thyroid, thymus, pituitary, testis, pancreas) has consistently failed to give a similar reaction. Small groups of large nerve-cells and sympathetic fibres running from them are frequently seen in the medulla of the rat's adrenal (Plate 4). In the adrenal of the mouse, however, nerve-cells and nerve-fibres are much less commonly seen.

When demonstrating these preparations the question has been frequently asked—What is the evidence that these fine black granules in the medullary cells are adrenalin ? The answer to this question is :

1. Osmic acid, which is generally regarded as a specific histochemical reagent for fats and lipoids, is blackened also by adrenalin *in vitro*.

2. The fine black granules rendered visible by this method are found only in the cells of the adrenal medulla and in no other endocrine organ. They are found in the

medullary cells of all the vertebrates examined. In other words, the reaction takes place in cells which contain adrenalin and in no other cell.

3. There are conditions under which the medullary cells lose their adrenalin as demonstrated by physiological or chemical methods or by the fading of the chromaffin stain. Under such conditions the cells are found empty of these granules.

4. Under certain conditions which will be discussed in the next chapter a secretion of adrenalin into the blood-stream has been demonstrated previously by various methods. Under these conditions a profound change in the cells of the medulla and a passage of the granules into the central vein can be demonstrated.

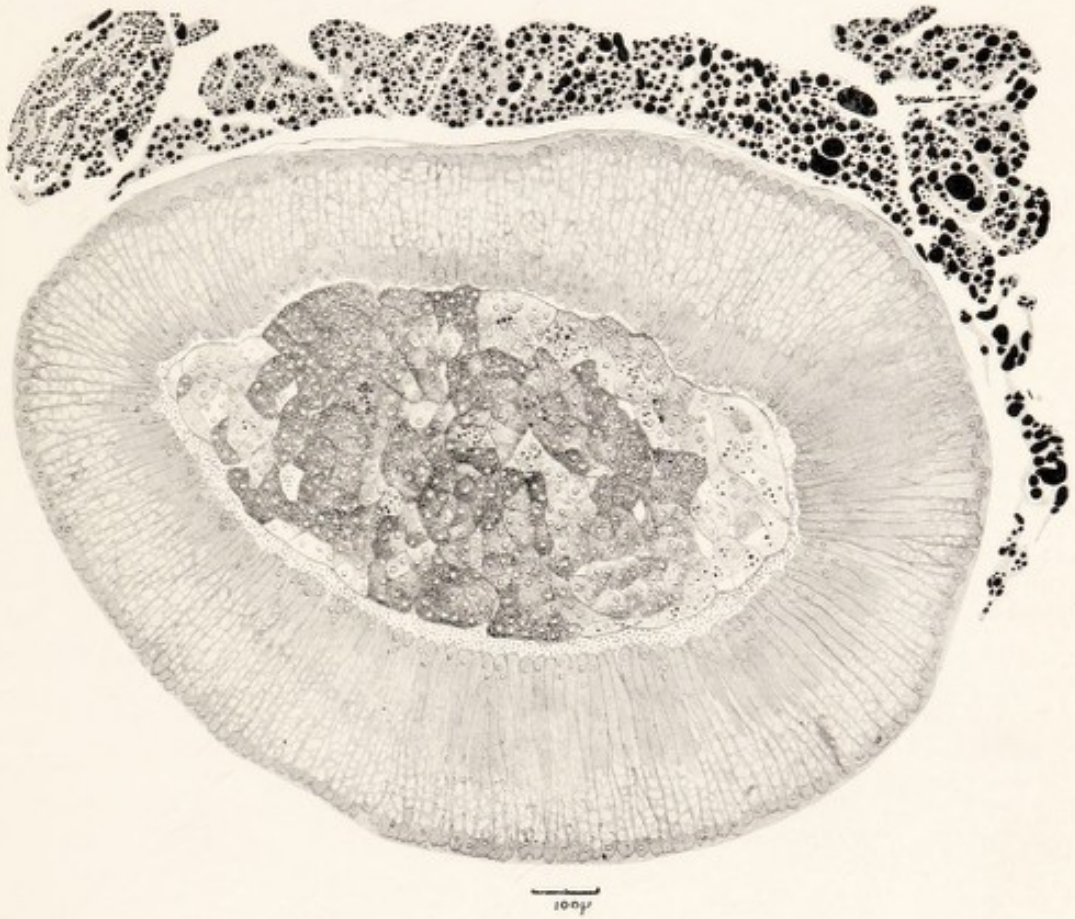

PLATE 1.

Low-power appearance of adrenal of normal mouse fixed in osmic vapour. The section through the central part of the gland illustrates the relative proportions of cortex and medulla in the mouse and the sharp separation between the two. The medullary cells fixed by this method exhibit two distinct appearances of black and of light cells, usually grouped together in alveoli. The lipoid granules of the cortex have been dissolved by the mounting medium (Canada balsam in xylol) and are represented by vacuoles. The drawings show the distribution of the lipoid in the resting gland. The zona reticularis is narrow. The peri-adrenal, or glandular, adipose tissue has retained the osmic stained-fat. $\times \frac{60}{1}$.

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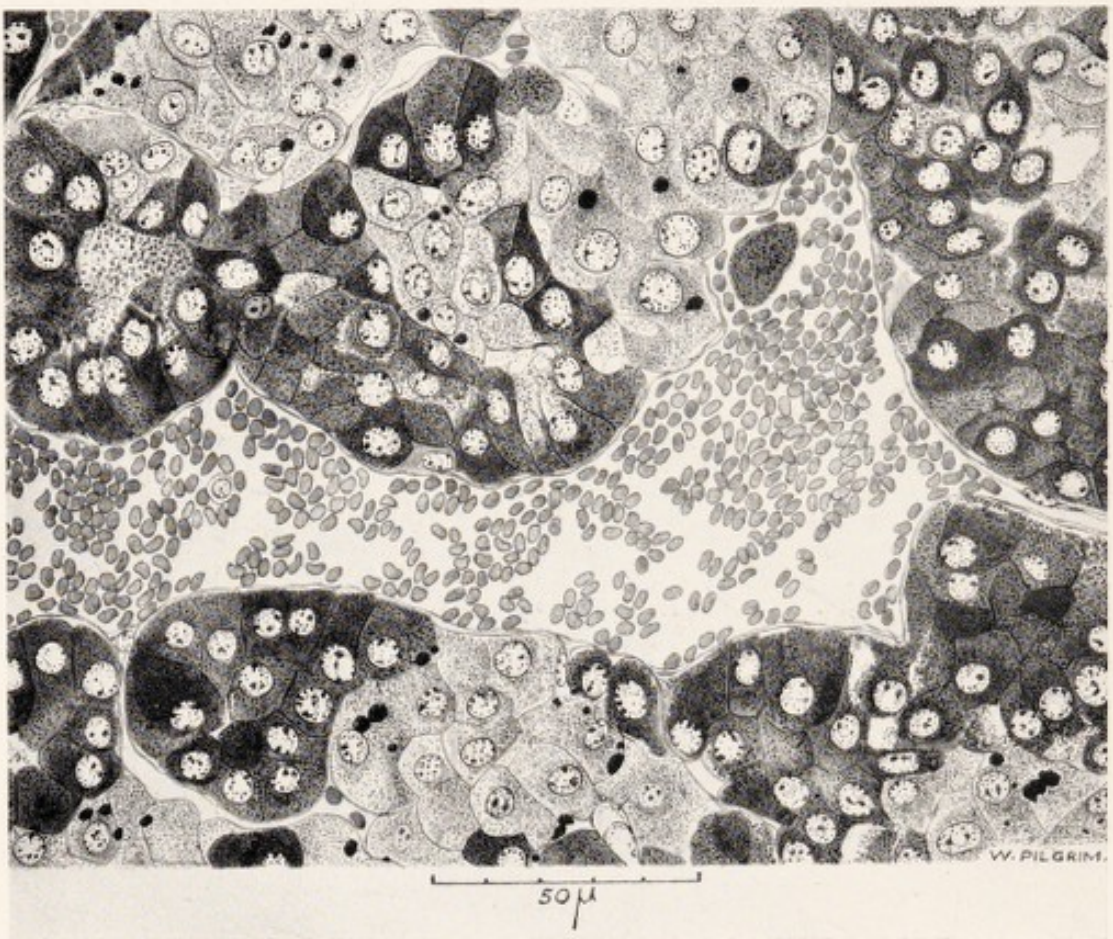

PLATE 2.

Adrenal medulla of normal mouse. Osmic vapour fixation. The drawing shows the central vein containing red blood corpuscles and the medullary cells surrounding it with their large clear turgid nuclei. Some of the medullary cells are deep black, being closely packed with the blackened granules of adrenalin ; others are a light grey with few granules of adrenalin but containing instead relatively large black " globoid bodies ". The " black " and the " light " cells are arranged together in groups of the same type of cell. The preparation represents a resting gland with no discharge of adrenalin. $\times \frac{500}{1}$.

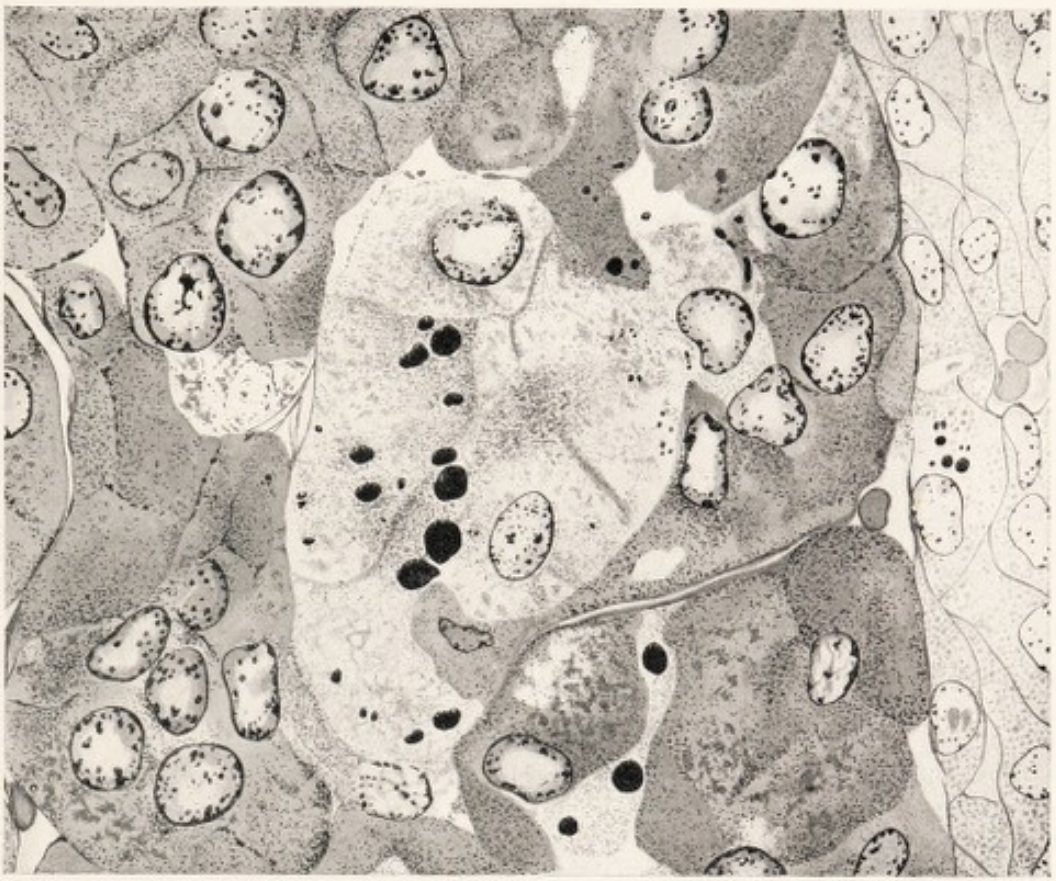

PLATE 3.

High-power view of adrenal medulla of mouse showing island of "light" cells with black "globoid bodies" surrounded by black medullary cells evenly filled with granules of adrenalin. The drawing is taken from the border of the medulla and cortex, of which the zona reticularis is represented on the right. The cells of the latter are swollen and contain a number of small black granules which are not fat or lipoid, but probably a precursor of adrenalin. The gland was taken from a mouse which had been kept in the cold for nine days and had remained well. $\times \frac{1100}{1}$.

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PLATE 4.

Adrenal medulla of rat. Osmic vapour fixation. The appearance of the medullary cells is essentially the same as that in the mouse. The drawing shows sympathetic nerve fibres running directly into a group of medullary cells. $\times \frac{600}{1}$.

CHAPTER III

THE ACTIVE ADRENAL GLAND

When a normal mouse is subjected to certain conditions the adrenal medulla becomes the scene of extraordinary changes at the climax of which an almost explosive activity is exhibited by the medullary cells. There are two conditions which induce these changes most readily, namely, exposure to cold and injections of a few milligrammes of β-tetrahydronaphthylamine ("T.H.N." for short)—a drug which produces a rapid hyperpyrexia. We shall describe first the appearance of the medulla twenty to forty minutes after the injection of 2 to 3 mg. of T.H.N. (Plate 5). The capillary spaces open up and become widely dilated, separating groups of alveoli ; the medullary cells become vacuolated and lose in varying degrees their content of adrenalin granules. In the cells adjacent to blood-vessels the adrenalin granules can often be seen being poured directly into the blood-vessel. The capillary blood spaces and especially the big central vein is filled with these black granules in the midst of which the red blood corpuscles are lying. Sometimes the change is so violent that the endothelial lining separating the lumen of the small veins from the cells bordering them is torn off and small parts of the cytoplasm are swept into the blood-stream, where they can be seen. Occasionally, the vacuoles forming in a group of cells which constitute an alveolus coalesce in the centre so as to form a lumen into which the adrenalin granules are secreted. The nucleus,

also, undergoes a remarkable change. It becomes deflated and collapses so that the large clear turgid nucleus of the resting cell is transformed into a small, dense, brown-stained structure, resembling in size and even in appearance a red blood corpuscle. In these cells in which the nucleus undergoes this collapse the cytoplasm also changes : it loses its granular structure and assumes a uniform laked appearance of the same brownish hue as the nucleus. Plates 6 and 7 reproduce a number of cells from an active gland in which all the stages of the nuclear change are represented. Other methods of fixation do not reveal this nuclear change very clearly. It can hardly be assumed that this change is peculiar to the nuclei of the adrenal medulla. It is more likely to be a process which though common to the nuclei of cells exhibiting great functional activity has escaped observation on account of unsuitable methods of fixation. So far as I am aware there is only one account in the literature by Carlier describing a similar change in the cells of the gastric mucosa at different stages of digestion.

The extraordinary change in the nucleus and cytoplasm of these " laked cells " does not involve the death of these cells. For if the gland is examined two to three hours after the injection, when the effect of T.H.N. has passed off, these cells recover : the nucleus swells and gradually assumes again its normal appearance, and the cytoplasm becomes charged with adrenalin granules. I have never seen mitotic figures in the medulla during this process of recovery. The preceding description gives only the most obvious changes taking place in the medulla and does not refer to the finer cytological changes. These demand a separate study, and the readiness with which the activity of the medullary cells can be aroused and controlled experimentally in the way just described opens up a promising method for the experimental investigation of those finer cytological changes in different stages of cellular activity. A pictographic summary of the prob-

able cycle of changes occurring in the medullary cells is given in Text Figure 1.

This massive, almost explosive, secretion of adrenalin by the cells of the medulla is reflected in the general effects of the drug, T.H.N., which can best be studied in larger animals (rabbits or rats) and which will be dealt with in greater detail in a later chapter, particularly with

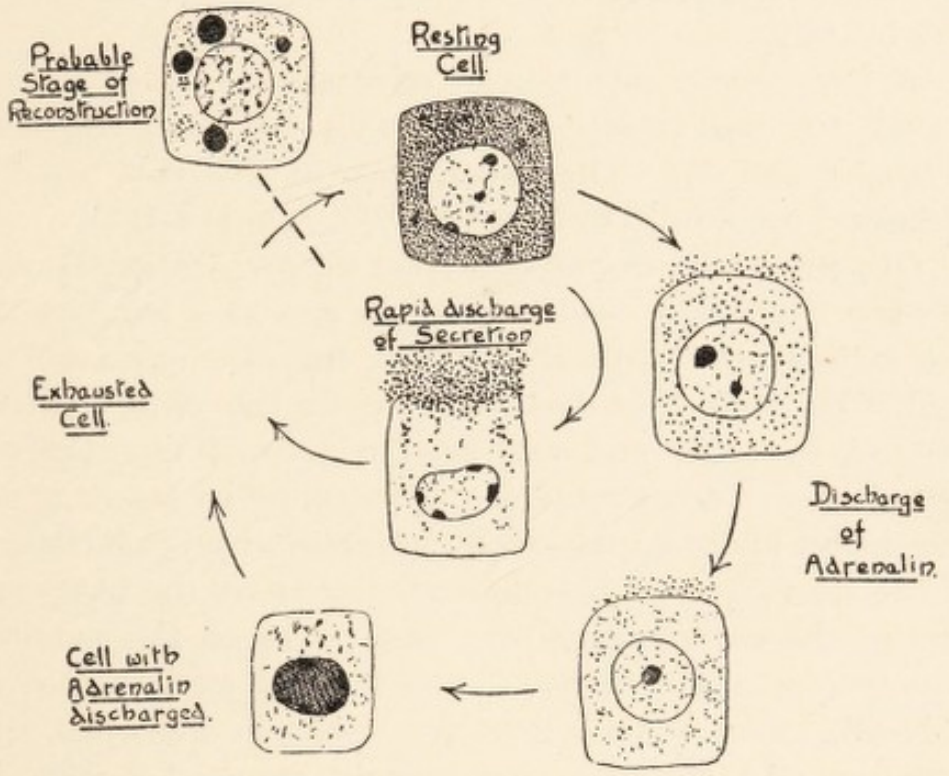

FIG. 1.—Pictographic summary by Dr. R. J. Ludford of the gross changes during the secretory cycle of the medullary cells of the mouse's adrenal.

reference to the way in which it produces a rapid rise in temperature. Here it is sufficient to state that about thirty to forty minutes after the injection of a suitably large dose of the drug into an unanæsthetised rabbit, the animal presents the typical picture of general sympathetic stimulation : rapid panting respiration, intense constriction of the arterioles, readily observed in the ears which feel cold to the touch, widely dilated pupil and protruding eyes and erection of the fur. In fact, the appear-

ance of such an animal is indistinguishable from that of an unanæsthetised animal after an injection of adrenalin, except that the effect of adrenalin is more rapid and more transient. If lethal doses have been given the animals die after T.H.N. with large widespread hæmorrhages into the lung just as they do after lethal doses of adrenalin. That this drug produces a diminution in the load of adrenalin in the medulla was demonstrated fifteen years ago by Elliott.

A very active secretion of adrenalin can also be induced by the injection of certain bacterial vaccines (Plates 6 and 7). The significance of this fact will be discussed more fully in Chapter VIII. (pp. 119-127).

Of even greater importance from the physiological point of view is another condition which acts as a stimulus to the cells of the adrenal medulla, namely, exposure to cold. This was first demonstrated by the histochemical method in 1916, and has been confirmed recently by means of the denervated pupil reflex. The intensity of the change in the adrenal medulla varies with the intensity of the stimulus, and this depends partly on the temperature of the environment, but partly also on the suddenness with which a change in the thermal environment is induced. Mice can be kept for weeks in the open air, even in cold weather, and remain in good health if they are kept in dry wooden boxes covered with a perforated zinc lid. The adrenal medulla of such animals show only slight changes and the cells are fully charged with adrenalin granules. Perhaps the most obvious change is seen in the zona reticularis. It is congested, and small round masses stained black with osmic acid make their appearance in some of the cells. These small round masses are, as already stated, not lipoid in nature, but resemble the globoid bodies seen in the light islets of the medulla and represent probably either adrenalin or a precursor of adrenalin. This conclusion has also been confirmed recently by Hartman. Plate 3 represents

the appearance of these globoid bodies in the cells of the zona reticularis in a mouse which had been kept for several weeks in the open air during cold weather. When a mouse has been kept in a warm room at about 18° C., and is then suddenly exposed to a cold environment, there is then a much more active secretion of adrenalin and the same changes can then be observed in the medullary cells which have already been described as occurring after T.H.N. Plate 8 is drawn from the adrenal of such an animal killed after an hour's exposure to moderate cold.

When the stimulation by cold is intensified by wetting the mouse and keeping it in an open glass jar in a cold room, so that the heat loss is greatly increased, the adrenal medulla responds even more actively to the stimulus by the massive secretion of adrenalin into the blood spaces. If the stimulus is sufficiently intense and sufficiently prolonged the animals are unable to maintain their body temperature and the adrenal medulla shows then an almost complete disappearance of adrenalin without any further secretion taking place. The gland is exhausted. Plates 9 and 10 represent these conditions in an exhausted gland of a mouse dying from exposure to cold. In rats Vincent has found a disappearance of the chromaffin reaction of the adrenal medulla under similar conditions.

Another experimental condition inducing a similar change in the adrenal medulla is anæsthesia. This is represented in Plate 11, taken from a mouse kept under ether for forty-five minutes without any further surgical interference. Since it is well known that anæsthesia produces a fall of body temperature and upsets the heat-regulating mechanism the animals were anæsthetised in a warm room and kept covered with cotton-wool, so as to minimise this effect as much as possible. A glance at the figure is sufficient to show that the mere process of anæsthesia introduces a serious fallacy into experiments, having as their object the demonstration of the response of the adrenal to certain stimuli. It has been

stated already that anæsthetics antagonise the action of adrenalin, when injected (see Chapter I. p. 6). It has also been shown that anæsthetics prevent the induction of sympathetic fever by β-tetrahydronaphthylamine. It is probable, therefore, that the secretion of adrenalin induced by anæsthetics is not a result of the stimulation of the gland by the anæsthetic, but a secondary effect resulting from the disturbance of heat regulation in anæsthesia. If ether or chloroform is used there may be an additional solvent effect on the cortical lipoid. Since anæsthetics tend to deplete the adrenal medulla this observation emphasises the importance of keeping the anæsthetised subject warm, so as to avoid the additional depletion imposed by cold.

The question whether asphyxia and oxygen deficiency produce a secretion of adrenalin has been the subject of a prolonged controversy. Plate 12 shows the appearance of the adrenal medulla of a mouse which has been made to breathe an atmosphere rich in carbon dioxide. It shows conclusively that this induces a secretion of adrenalin. On the other hand, I have never been able to obtain convincing evidence of a secretion of adrenalin as the result of a deficiency in oxygen resulting from exposing mice for a short time to a diminution in the pressure of air sufficient to induce severe symptoms.

The injection of insulin does not stimulate the adrenal medulla of mice to increased activity if the onset of hypoglycæmic convulsions is prevented by the simultaneous injection of glucose or by giving the injection after a meal. It may be absent even in mice dying in hypoglycæmic convulsions (Plate 13). If a secretion of adrenalin occurs at all in this latter condition, it is therefore not a primary but a secondary effect, the adrenal being stimulated by the fall in temperature or perhaps the hypoglycæmia. Our observations confirm the findings of Stewart and Rogoff, who also failed to demonstrate an output of adrenalin after insulin, and

justify the criticism applied by Stewart to Cannon's method of using the denervated heart as an indicator of adrenal activity. Using this latter method Cannon obtained evidence of adrenalin secretion after insulin.

The thyroid hormone on the other hand has a definite effect, which is, however, very complex. The subject will be dealt with later, in discussing the interrelationship of the thyroid and adrenal glands (Chapter VII.).

One striking feature of the activity of the adrenal medulla is that the activity does not extend uniformly over the whole gland. The changes which we have described and figured are most pronounced in the neighbourhood of the central vein and its larger tributaries. They may be proceeding there very actively while the opposite pole of the medulla exhibits very little evidence of increased activity. Even in those parts of the medulla where the changes are actively proceeding the various cells do not participate equally. It is a fact of general biological importance that when an organ is stimulated to increased physiological activity the individual cells or cell-groups do not equally participate in that activity. Khanolkar, working in Boycott's laboratory, has first demonstrated this principle for the kidney and has adduced as further confirmation the behaviour of the mouse's adrenal after stimulation by cold as demonstrated by our preparations.

So far we have dealt only with changes in the medulla. But the cortex participates in the activity of the medulla. When the latter is stimulated to activity the zona reticularis of the cortex becomes congested. We have already referred to the appearance of the black globoid bodies, which represent either adrenalin or at least its precursor, in the cells of this zone. In addition there is a change in the distribution of the cortical lipoid giving the impression that the lipoid is being swept from the periphery of the cortex towards the centre, *i.e.* towards the medulla. At any rate, one finds under these conditions

large globules of lipoid in the cells of the zona reticularis which in a normal resting gland are free from lipoid. These large black globules are, however, not always entirely composed of lipoid material. For when the section is treated with turpentine to remove the blackened globules of fats and lipoids, one finds sometimes only parts of these globules dissolved, leaving behind a reticulate framework which still retains its osmic acid stain. These big masses in the zona reticularis can also be seen occasionally in sections of adrenals of animals or of man, prepared by the ordinary histological methods, when they have a mulberry-like appearance. In conditions of extreme activity the movement of the lipoids from the periphery of the cortex towards the centre, which accompanies activity of the medulla, may sometimes actually carry the lipoid into the medullary cells adjoining the cortex, although normally lipoid is never seen in a cell containing adrenalin granules. Plates 14 and 15 illustrate these conditions. They have been obtained from a mouse after exposure to cold, and represent the same preparation before, and after, treatment with turpentine. These figures show that under these conditions lipoid material is mixed up with non-lipoid material which also blackens with osmic acid : the appearance indicates that when the gland is stimulated to activity and adrenalin is being actively poured out into the blood-stream, adrenalin or its precursor is being formed in the cortex, and they even suggest the possibility that some constituents of the cortical lipoids may be concerned in this process. This migration of the cortical lipoid towards the medulla has also been observed in bacterial infections—a point with which we shall deal in a subsequent chapter.

This process leads to a consideration of the way in which the cells of the medulla are recharged with adrenalin after they have been stimulated to active secretion. A number of experimental observations are on record which agree in showing that this process must be an exceedingly

active and rapid one. The ingenious experiments of Stewart and Rogoff have shown that stimulation of the splanchnic nerve which induces a secretion of adrenalin does not lead to a diminution in the load of adrenalin in the medulla of the stimulated gland, even when secretion is induced many times by repeated stimulation. Our observations confirm these conclusions. When, by a stronger stimulus, a temporary depletion of the medulla can be effected, the medulla is recharged within an hour or two after the stimulus has been withdrawn. It follows, therefore, that the stimulation of the gland to secrete adrenalin is also a stimulus for the formation of adrenalin. The amount of adrenalin present in the medulla at a given moment — the " load " of adrenalin — is therefore, as Stewart and Rogoff were the first to point out, only the difference between the rate at which adrenalin is secreted and the rate at which it is formed. An active gland may therefore be associated with a high or with a low " load " of adrenalin, and conversely an inactive gland may have a high load, or when the inactivity is due to exhaustion of the medulla it may have a low load. Estimation of the load of adrenalin is therefore not a reliable indicator of the activity of the gland.

As already stated, the efficacy of cold as a stimulus does not depend so much on the temperature itself as on the change in the temperature. Thus the adrenal of a mouse which has been kept for a long time in a warm room at a temperature around 20° C. will show active secretion as soon as the animal is subjected to a temperature of about 5° C. But when it is kept at that temperature for a week or two weeks, the adrenal will again assume more the appearance of a resting gland. The function of the adrenal in heat regulation enables the organism to adapt itself *rapidly* to sudden changes in the thermal environment. Once the organism has been tided over such a sudden change it maintains its adaptation to the altered thermal environment by some other mechanism,

possibly the thyroid gland. We shall see later in dealing with the effect of climate on the human organism that a great importance attaches to the variability in the thermal environment. We shall also see later (see Chapter VII.) that exposure to heat which inhibits the activity of the adrenal gland leads to a disappearance of the cortical lipoid and that a similar disappearance of the cortical lipoid may also occur in the course of certain (but not all) bacterial infections. It will be convenient if we state briefly here the conclusions which will be deduced in later chapters from the effects of experimental changes in thermal environment: activity of the gland is accompanied by a spreading of the cortical lipoid over the cortex, inhibition of the gland by a disappearance of the cortical lipoid.

The study of the adrenal gland as an endocrine factor in heat regulation emphasises the essential unity of the gland: cortex and medulla function together so far as responses to changes in the thermal environment are concerned and not as two separate organs. It is indeed difficult to understand how the medulla could ever be stimulated to increased activity without the cortex participating in it. As in all organs an increased activity of the medulla is accompanied by an increased blood flow through the medulla. Now the vascular arrangement in the adrenal is such that the blood must first pass through the cortex before it reaches the medulla, so that an increased blood flow through the medulla must necessarily be accompanied by an increased flow through the cortex. On the other hand, it is conceivable that there may be an increased blood flow through the cortex in which the medulla does not participate, since the blood may flow round the medulla through the vascular zona reticularis. The cortex may therefore conceivably work independently of the medulla, but the medulla cannot work independently of the cortex.

It is a very striking fact that as we ascend the evolu-

tionary scale in the vertebrates we are accompanied by a characteristic change in the anatomical relationship of the two histogenetically distinct tissues which in the mammals form the cortex and medulla of the adrenal gland. We know from the work of Cohn that the cortex is derived from inter-renal tissue and the medulla from para-sympathetic ganglion cells. The anatomical relationship of these two tissues varies throughout the vertebrates, but all vertebrates have this in common that groups of para-sympathetic ganglion cells acquire the power to form, store and discharge adrenalin. Since these adrenalin-containing cells give a characteristic brown reaction with solutions of potassium bichromate they are usually described as " chromaffin cells ".

In fishes such groups of chromaffin cells and groups of inter-renal tissues are separate. In amphibians they come into contact, small groups of the adrenalin-containing cells being placed on the surface of a mass of inter-renal tissue. In reptiles the groups of adrenalin-containing cells have fused together and surround the inter-renal tissue. In birds the adrenalin-containing cells not only surround the inter-renal tissue but penetrate into it and are scattered throughout it in strands. Lastly, in mammals the adrenalin-containing cells are collected to form one mass—the medulla—in the centre of the inter-renal tissue which surrounds it as the cortex of the gland.

This parallelism between the evolution of the adrenal gland and of the heat-regulating mechanism must not, however, be interpreted as indicating that the heat regulation of warm-blooded animals is due entirely to the adrenal gland. The basis of the heat-regulating mechanism in mammals is the sympathetic nervous system. The thyroid-adrenal apparatus, in so far as it produces positive effects, acts by playing on the sympathetic nervous system and fails to do so if the latter is destroyed. Thus in mammals interference with the thyroid-adrenal apparatus by experimental removal of the glands or diseases, such

as myxœdema or Addison's disease, which impair the functional activity of the glands, merely impair the efficiency of the heat-regulating mechanism, but the organism does not completely lose its power to maintain its temperature above that of the environment. This power is lost, though not completely, after certain nervous lesions localised in such a way that they affect the whole sympathetic nervous system (see Chapter V.).

If we return now to the change in the anatomical interrelationship of the two constituent tissues of the adrenal gland accompanying the evolution of the vertebrates, we cannot help being struck by the parallelism which exists between this change and the development of a heat-regulating mechanism which renders the body temperature independent of the temperature of the environment. This mechanism is fully developed in birds and in mammals, but appears for the first time in reptiles, though only in a very incomplete form. Reptiles are usually classed as cold-blooded animals, but observations are on record which show that under certain conditions they are able to raise their temperature considerably above that of their environment. Valenciennes was the first to record the fact that pythons, when coiled round their eggs during incubation, maintain a temperature as much as 20° above that of the surrounding air, although they take no food and little exercise during this period. This has been repeatedly confirmed, and a temperature of 35·6° C. has been recorded in a female python when the air temperature was only 15·6°.

These considerations of comparative anatomy again emphasise the synergy of cortex and medulla. It is not the mere presence of groups of cells containing adrenalin which confers upon the adrenal the power to act as an efficient endocrine factor in the heat regulation of the body. If the adrenal is to be an efficient factor in heat regulation it must be able to respond rapidly to changes in the thermal environment, not only by a secretion of

adrenalin, but also by a rapid new formation of adrenalin. We have seen that the cortex participates in the new formation of adrenalin, and the considerations of comparative anatomy suggest that the anatomical arrangement of cortex and medulla in the higher vertebrates ensures a rapid new formation of adrenalin when the medulla is stimulated to increased activity.

Interesting problems of comparative physiology are opened up if we raise the question how alterations in the thermal environment affect the thyroid-adrenal apparatus in the different groups of vertebrates. We know that the metabolism of cold-blooded animals diminishes in intensity as their thermal environment falls, while that of warm-blooded animals increases under these conditions. This suggests that the activity of the thyroid and adrenal glands of cold-blooded animals is also diminished under these conditions. In warm-blooded animals exposure to cold is a powerful stimulus to the activity of these glands. If in cold-blooded animals exposure to cold diminished the activity of these glands as it does that of all the other organs, the interesting conclusion would follow that in the course of evolution the response to an environmental stimulus in a specific group of cells has been completely reversed although these cells themselves have not changed their specific character.

Summary.

The histochemical method reveals the details of active secretion of adrenalin into the blood. This process of secretion is described and figured. At its height it is one of extraordinary, almost explosive, activity. In this way it is possible to obtain direct and conclusive evidence as to the conditions which stimulate the adrenal gland to active secretion. The conditions which have been specially studied are asphyxia, ether anæsthesia, injection of the drug tetrahydronaphthylamine, bacterial vaccines

and exposure to cold. The latter stimulus is effective, not only in relation to the temperature as measured by the thermometer, but also to the suddenness of the change in the thermal environment. Oxygen deficiency and insulin alone were not found to induce an active secretion.

The secretion of adrenalin by the medullary cells is accompanied by changes in the cortex, which manifest themselves by a movement of the lipoid from the periphery to the centre. Stimulation of the adrenal gland to secrete adrenalin is also a stimulus for the formation of adrenalin. In this later process, which is very rapid, the cortex takes an active part. The " load " of adrenalin in the medulla is, therefore, the balance between the rate at which adrenalin is formed and that at which it is secreted. The load of adrenalin is not a reliable indicator of the activity of the gland.

The study of the response of the adrenal to changes in the thermal environment and to other stimuli emphasises the functional unity of medulla and cortex. It is pointed out that in ascending the evolutionary scale in the vertebrates a close parallelism can be established between the anatomical relationship of cortex and medulla and the evolution of a heat-regulating mechanism.

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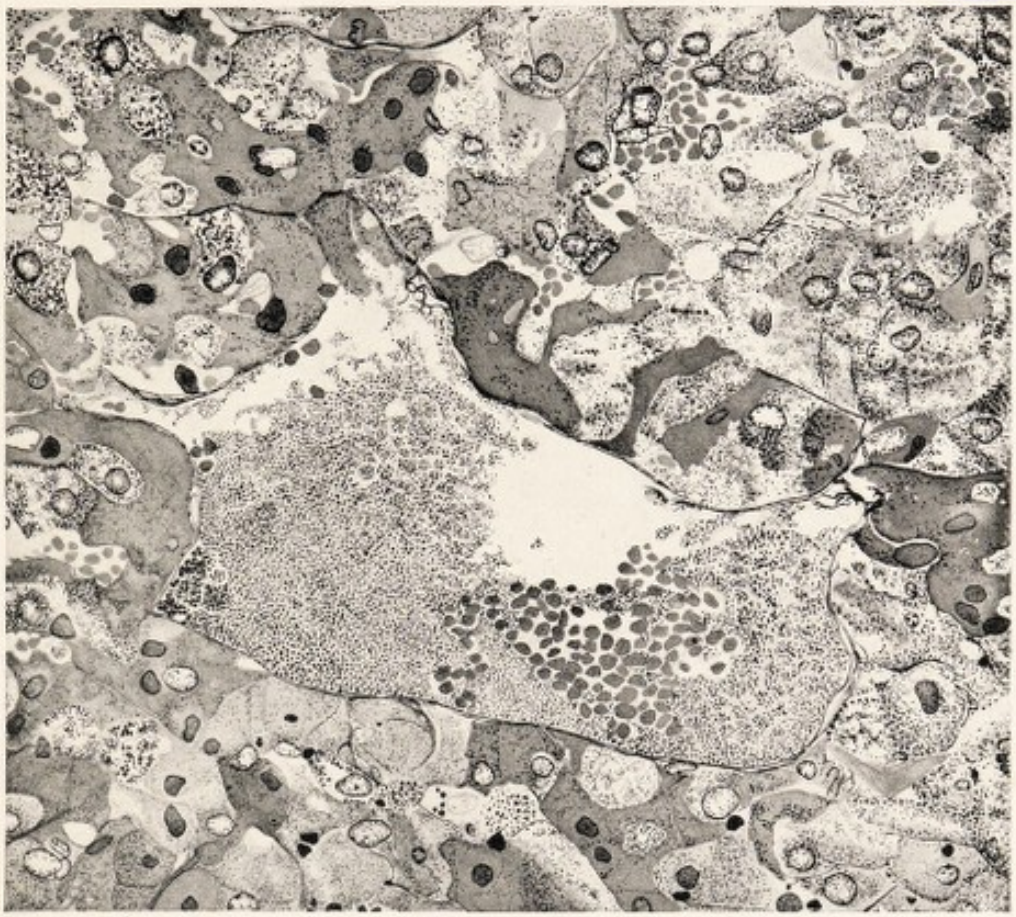

100 μ

PLATE 5.

Adrenal medulla of mouse which died forty minutes after injection of 2·5 mg. of T.H.N. The gland was swollen and congested. The figure shows a large tributary of the central vein into which the fine blackened granules of adrenalin are being discharged. The cells are extensively vacuolated and many exhibit a "laked" appearance of the cytoplasm with shrunken glazed nuclei. The figure represents a condition of intense activity of the gland. $\times \frac{480}{1}$.

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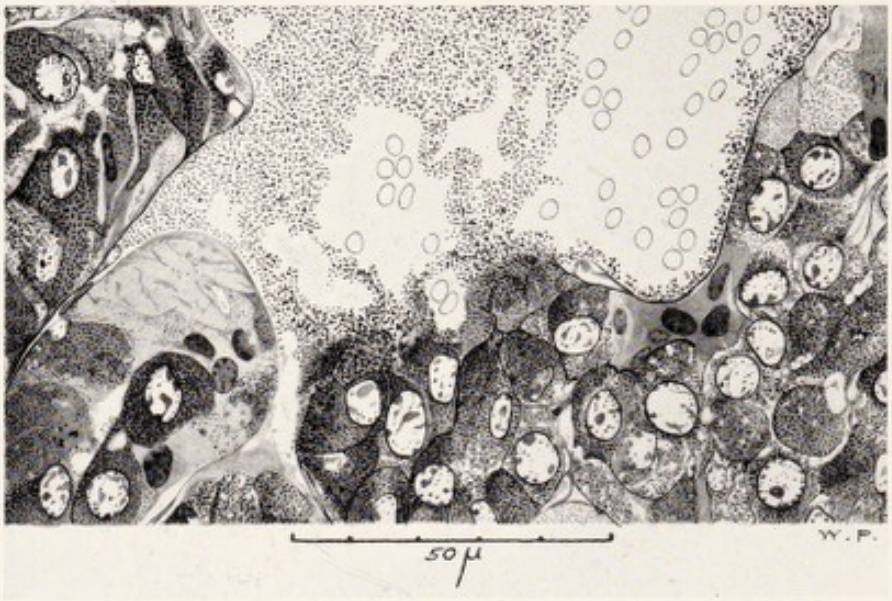

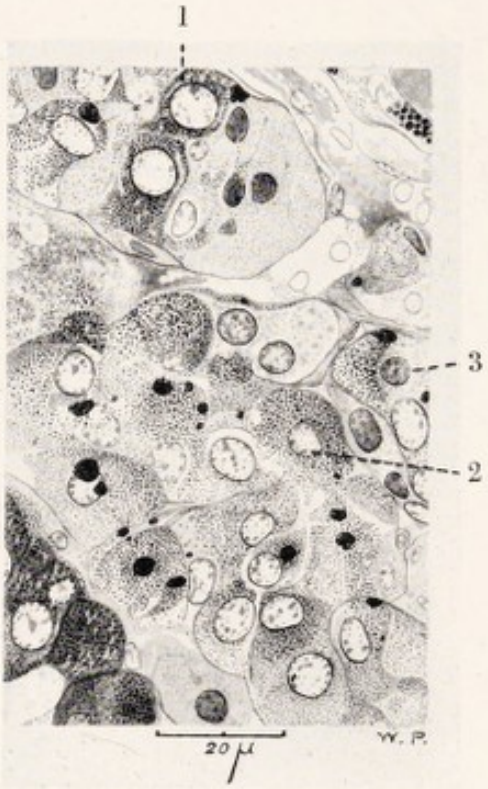

PLATES 6 and 7.

Different parts of the mouse's medulla showing phases of activity. Plate 6 shows the explosive discharge of adrenalin granules from the cells bordering a vein into the blood-stream with vacuolisation and laking of cells. Plate 7 shows different stages in the collapse of the nucleus accompanying the discharge of adrenalin. 1 = turgid normal nucleus, 2 = nucleus beginning to collapse, 3 = darkly stained nucleus, collapsed. $\times \frac{600}{1}$.

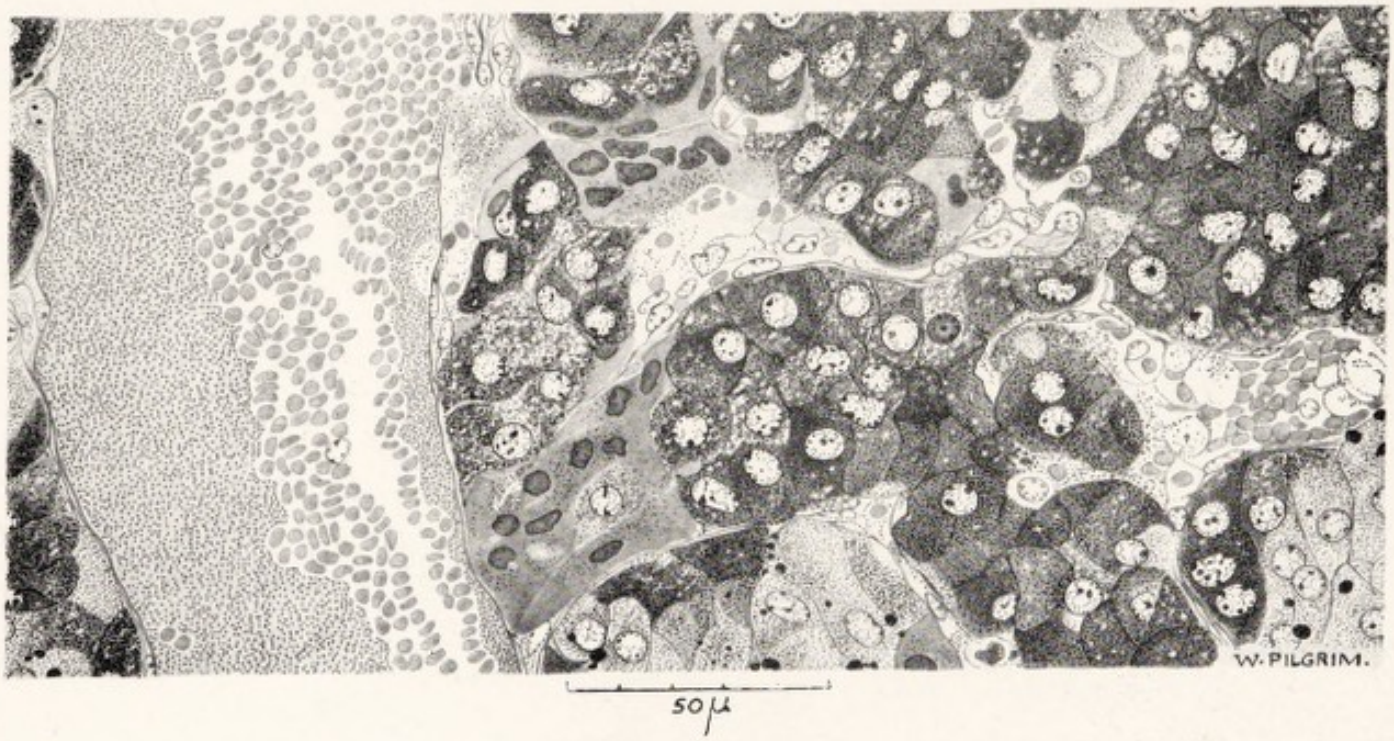

PLATE 8.

Discharge of adrenalin resulting from brief exposure to moderate cold. The drawing shows all the different phases of medullary activity: vacuolisation and laking of cells, opening up of capillaries, presence of adrenalin granules in central vein. $\times \frac{500}{1}$.

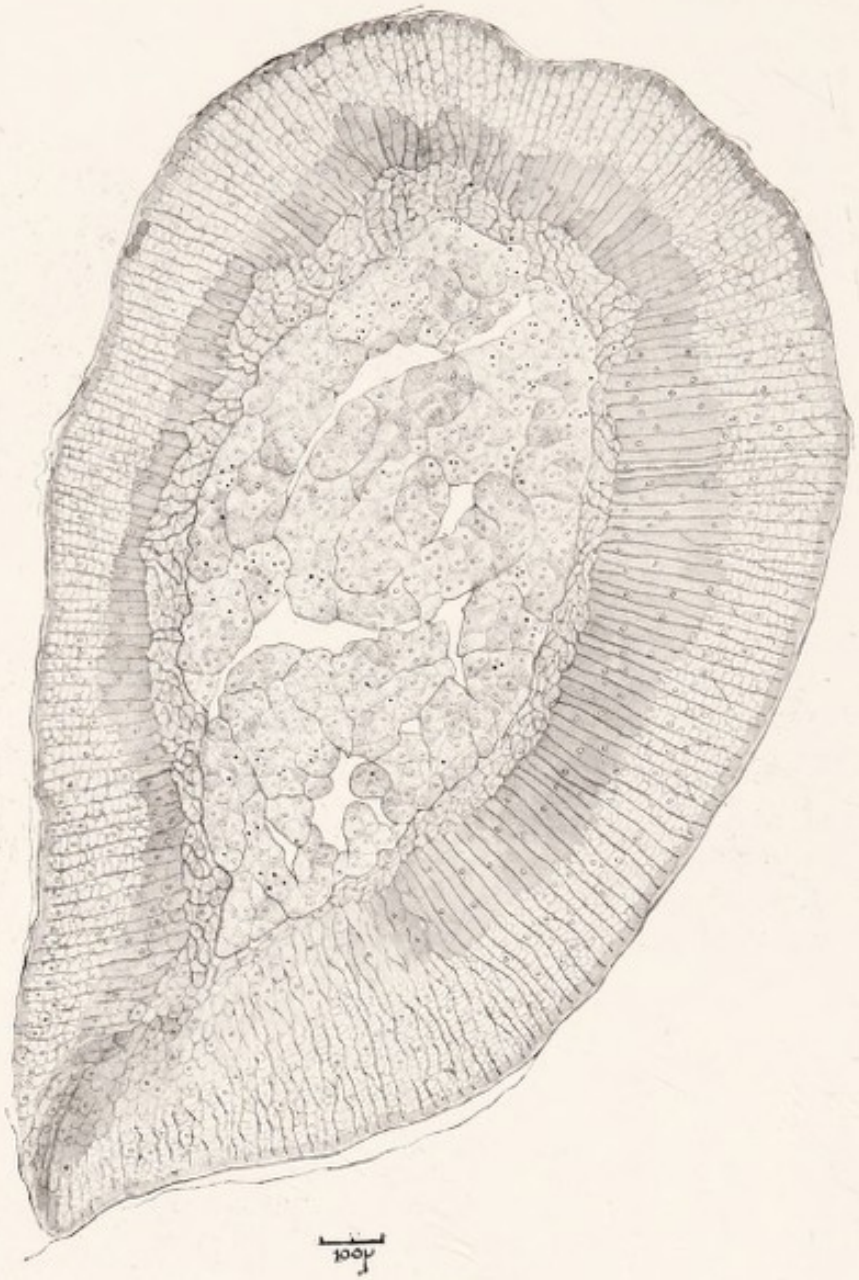

PLATE 9.

Exhausted adrenal of mouse dying, as the result of exposure to wet and cold for four hours, with subnormal temperature. The medullary cells show an almost complete absence of fine black granules of adrenalin. The cortical lipoids are not obviously diminished. They are represented in the drawing by vacuoles. $\times \frac{60}{1}$.

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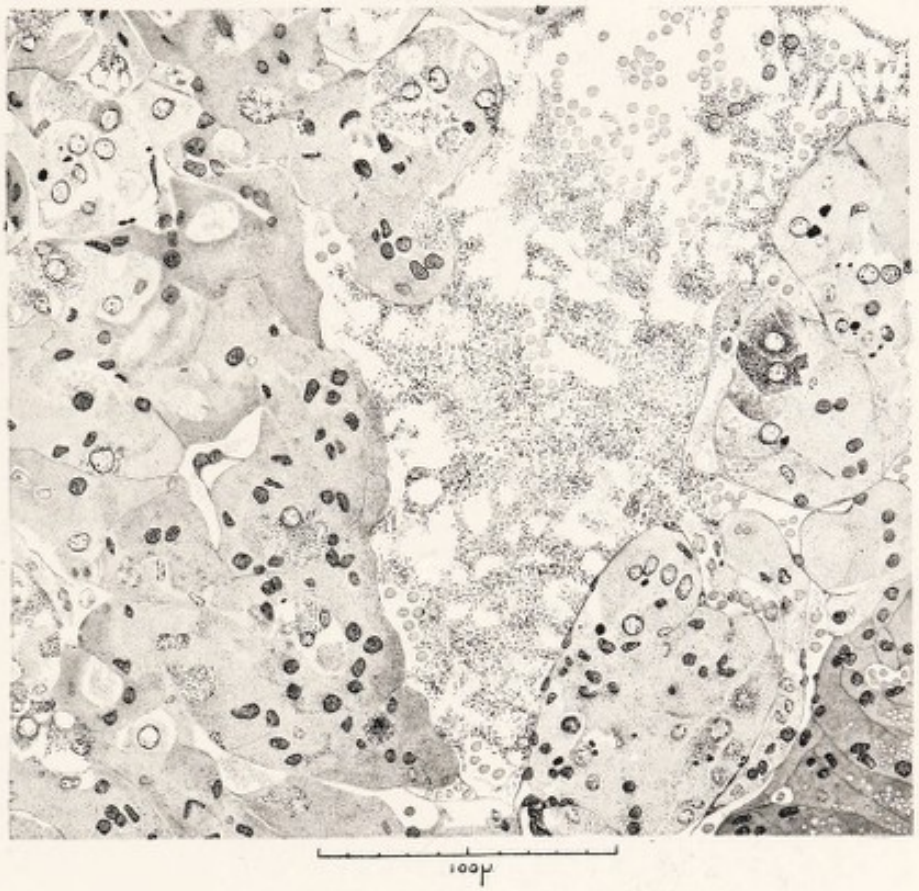

PLATE 10.

High-power view of adrenal medulla of mouse which became collapsed after exposure to cold and wet for one hour, revived by application of warmth for two hours, again exposed to cold for one hour and killed. Many medullary cells are laked, with shrunken glazed nuclei. The medullary cells with clear turgid nuclei are deeply vacuolated and have discharged most of their adrenalin granules. The lumen of the vein contains fine black adrenalin granules mixed with the plasma. $\times \frac{480}{1}$.

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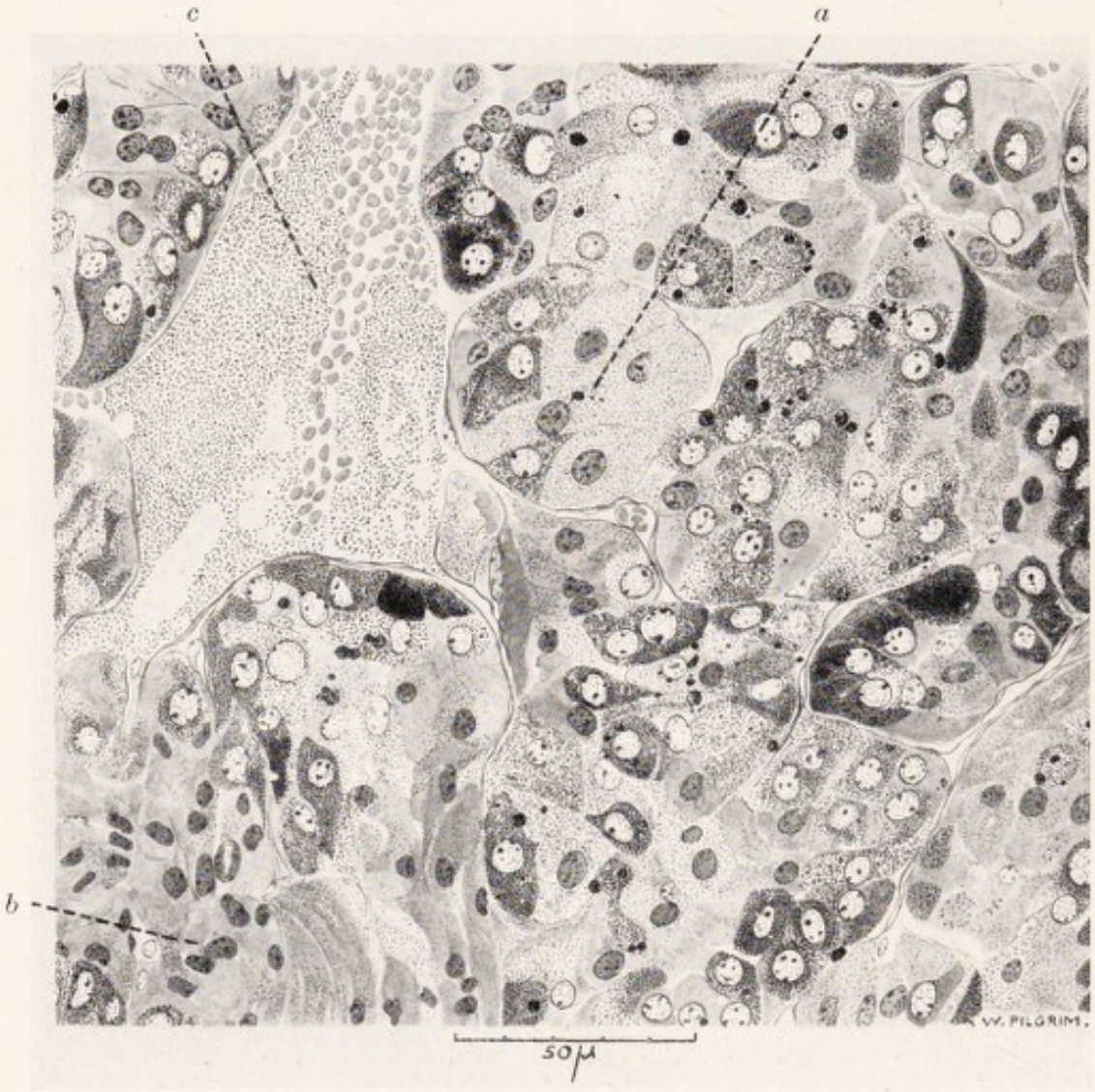

PLATE 11.

Discharge of adrenalin in ether anæsthesia. Adrenal medulla of mouse kept under ether for forty-five minutes. The drawing illustrates all phases of activity of medullary cells: (*a*) alveolus of medullary cells in different stages of discharging their content of adrenalin granules; (*b*) group of completely laked cells; (*c*) central vein filled with adrenalin granules. $\times \frac{470}{1}$.

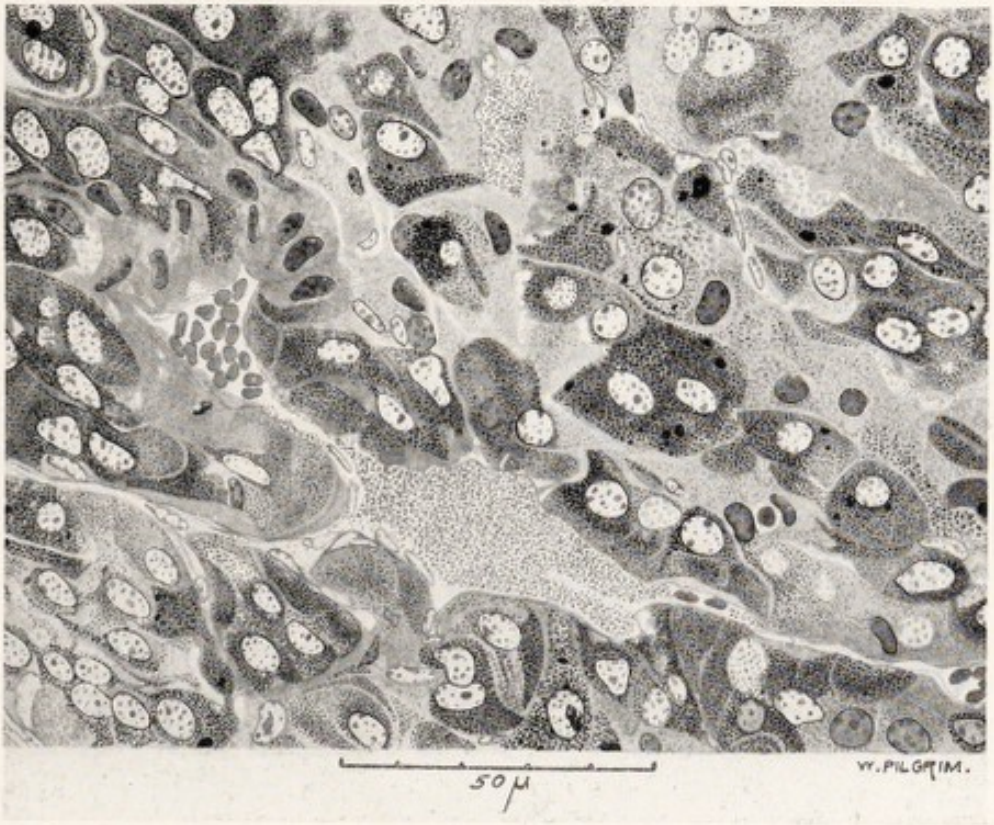

PLATE 12.

Discharge of adrenalin in asphyxia. Adrenal medulla of mouse killed by breathing an atmosphere rich in carbon dioxide. The drawing shows medullary cells in different phases of activity and a small venous space filled with granules of adrenalin. $\times \frac{580}{1}$.

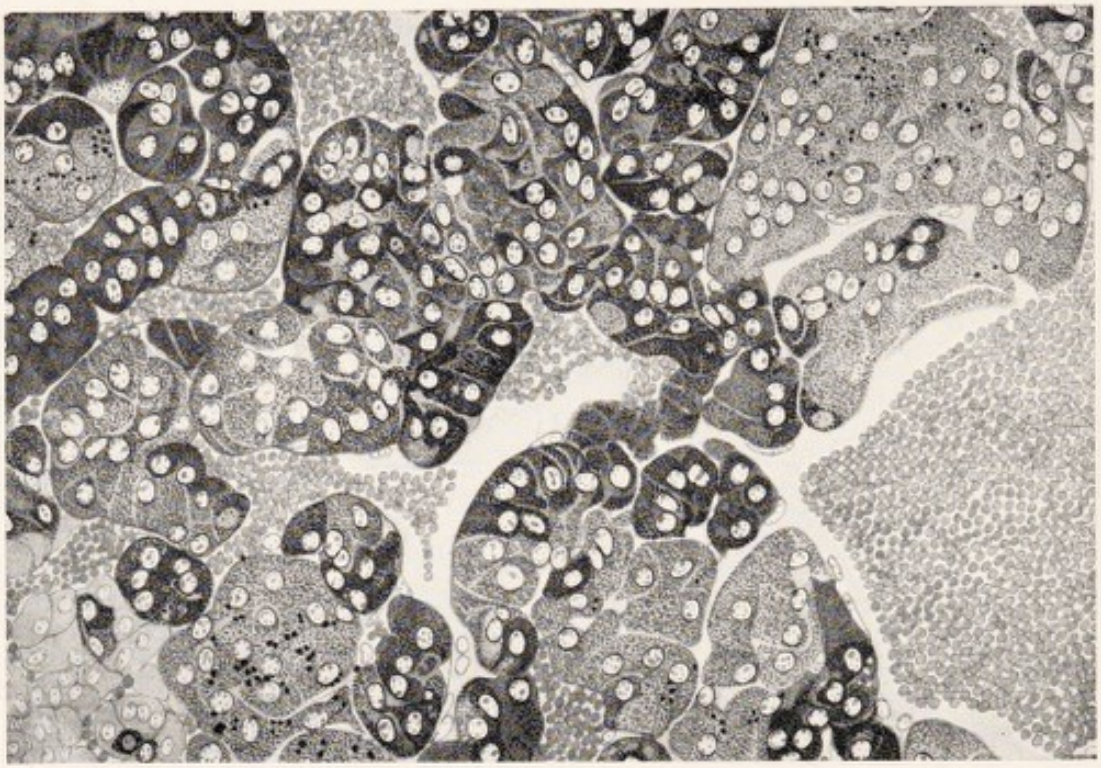

PLATE 13.

Effect of insulin. Adrenal medulla of mouse killed in hypoglycæmic collapse. There is great dilatation of venous blood spaces which are filled with red blood corpuscles; but the medullary cells give no indication of active secretion of adrenalin and no adrenalin granules are seen in the blood-vessels. $\times \frac{300}{1}$.

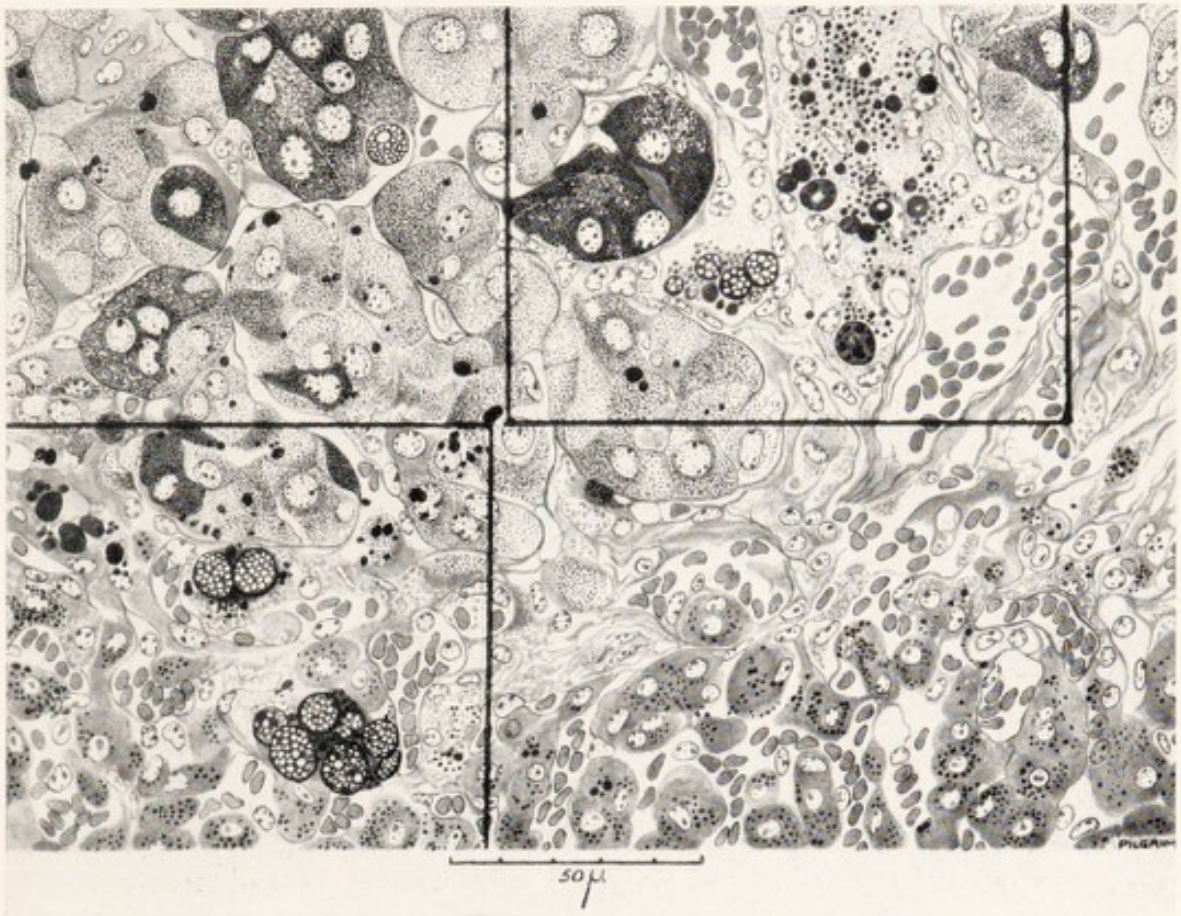

PLATE 14.

Junction of medulla and cortex in adrenal of mouse stimulated to activity by repeated exposure to cold. The right and left lower quadrants represent mainly the zona reticularis, which is congested and the cells of which are swollen. A few cells are filled with large masses of blackened reticulated globules consisting mainly of lipoid material. There are also cells containing small blackened globules not lipoid in nature. The right upper quadrant, which belongs to the medulla, shows the presence of lipoid material in medullary cells as an exceptional occurrence after prolonged activity of the gland. $\times \frac{490}{1}$.

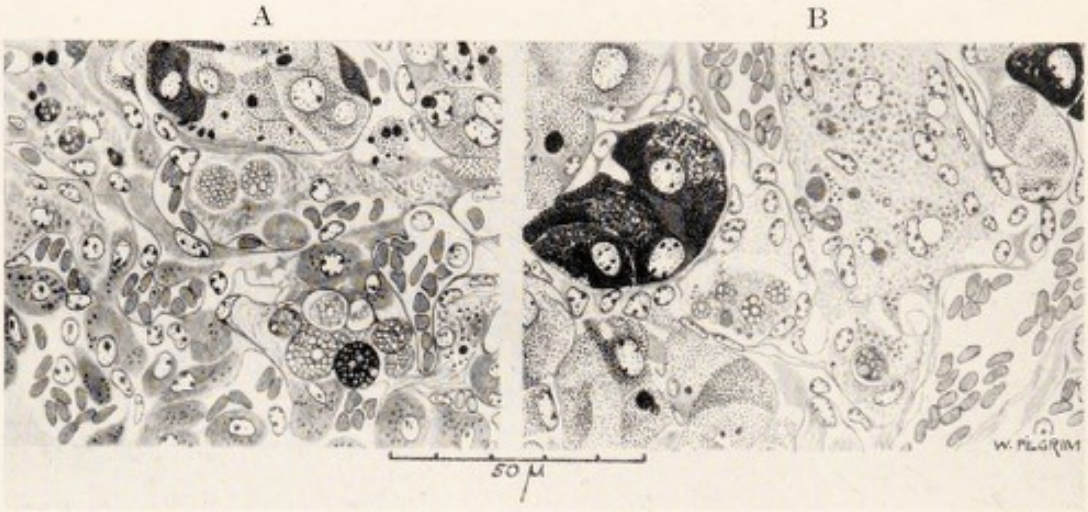

PLATE 15.

A, the left lower, and B, the right upper quadrant of Plate 14 after prolonged treatment with turpentine, which has bleached and dissolved the blackened lipoid material, but which does not dissolve adrenalin or blackened material other than lipoid. Drawing A shows that though the bulk of the reticulated globules has been dissolved by turpentine, and consisted therefore of lipoid material, some portions of these globules have resisted the action of turpentine and are therefore not lipoid in nature. Drawing B shows that most of the blackened material in the medullary cells was lipoid in nature and has been dissolved by turpentine. $\times \frac{490}{1}$.

CHAPTER IV

THE THYROID GLAND

At first sight the sphere of action of the thyroid gland appears to be entirely different from that of the adrenal. The outstanding feature revealed by experimental investigations of the thyroid hormone is its powerful action on metabolism, while immediate effects on blood pressure, heart, involuntary muscle are absent after an injection of thyroid extracts. With adrenalin the conditions are reversed. Here the immediate effects on blood pressure, heart and involuntary muscle are so striking that they have monopolised the attention of workers, while the importance of the adrenal gland as an endocrine factor controlling metabolism was not recognised until recently. The reason for this apparent difference in the sphere of action of the two glands is that the action of the thyroid hormone is slow, slight but lasting, while that of adrenalin is rapid, strong but very transient. We shall see that the condition produced by the increased activity of the two glands is essentially the same, namely, a stimulation of the sympathetic. An increased activity of the adrenal gland produces the same " sympathetic effect " on metabolism as an increased activity of the thyroid gland. Conversely, thyroid feeding as studied in man produces many of the symptoms of sympathetic stimulation as induced by adrenalin. Tachycardia, dilatation of the pupils with prominence of eyeballs and the concomitant widening of the palpebral fissure and perspiration are symptoms which have been observed in man after over-

dosing with thyroid and have sometimes been induced by malingerers for a special purpose, by taking large doses of thyroid gland over a long period. It must be admitted that experiments on anæsthetised animals have so far not yielded conclusive evidence either of a direct stimulation of the sympathetic by thyroid extracts or of an increased sensitivity of the sympathetic towards adrenalin. In such experiments not sufficient account has been taken of the slow action of the thyroid hormone, and of what is an even more disturbing factor, the use of an anæsthetic.

It is not yet sufficiently realised to what an extent anæsthetics interfere with observations on the sympathetic. They produce an enormous depression of the sensitiveness to stimuli of the sympathetically innervated organs. This can be demonstrated by a simple experiment in which a moderate dose of adrenalin, for instance 1 c.c. of 1 : 20,000 adrenalin, is injected into an unanæsthetised rabbit and a rabbit under ether or urethane. The difference between the two animals is striking. The normal rabbit shows all the symptoms of sympathetic stimulation in a most obvious manner : bulging eyes, dilated pupils, erection of the fur, forcible panting respiration, constriction of the arterioles in the ear, which is pale and cold to the touch. The anæsthetised rabbit shows with the dose mentioned no effect on the respiration or on the fur ; in fact, little beyond constriction of the arterioles in the ear and dilatation of the pupil. Moreover, in the unanæsthetised rabbit the effect lasts much longer than in the animal under an anæsthetic. Professor Lovatt Evans and I have succeeded in recording the respirations of a rabbit after adrenalin, both without and with the use of an anæsthetic (urethane). Adrenalin apnœa could be induced in a rabbit without anæsthesia with a dose of 1 c.c. adrenalin of 1 : 20,000. The same rabbit anæsthetised immediately afterwards gave no apnœic response to adrenalin until the enormous dose of

1 c.c. of adrenalin of 1 : 5000 was injected, and then the effect was less marked and more transient. Perhaps the most convincing evidence of the limitations imposed upon the study of the sympathetic and of the adrenals, in particular by the use of anæsthetics, may be found in the fact that anæsthetics impair the normal mechanism of heat regulation. In spite of the large amount of experimental work done on the functions of the adrenals, the fundamental fact that cold is a stimulus to the adrenal could only be demonstrated by the use of methods which excluded the use of anæsthetics.

In view of the slighter action of the thyroid hormone these considerations apply with even greater force to the investigation of the functions of the thyroid gland. Here too direct observations on the changes in the thyroid gland, when the unanæsthetised animal is placed under different experimental conditions, offer the most likely way to obtain conclusive evidence. Unfortunately, there is as yet no microchemical method available for the thyroid hormone. For the study of the functional activity of the thyroid gland we are at present dependent on the interpretation of changes in the gland to be observed by ordinary histological methods when the organism is subjected to a number of different conditions. On the other hand, investigations into the functional activity of the thyroid gland are facilitated by the fact that in this endocrine organ the specific secretion is contained in the "colloid" which accumulates outside the thyroid cells and is readily demonstrated by ordinary histological methods.

One of the most outstanding changes occurring in an organ exhibiting increased functional activity is an increased blood flow which is associated with an opening up of capillaries. This, as will be seen presently, is a very striking feature of the thyroid gland when a warm-blooded animal is subjected to exposure to cold or when "sympathetic fever" is induced. Under these two con-

ditions other changes may be observed in the thyroid gland, namely, differences in the size of the alveoli, with corresponding changes in the shape of the cells lining the alveoli and in the amount of colloid present in the alveoli, differences in the staining reaction of the colloid, irregularities in the shape of the alveoli, desquamation of the cells lining the alveoli and the appearance of red blood corpuscles among the colloid. Attention has also been paid to the condition of the mitochondria and of the Golgi apparatus in the lining cells.

Almost all our observations were made on the thyroid glands of the rat and the mouse. For purposes of comparison it is necessary to use the same fixative. We have used Schridde's fixation in formol-bichromate followed by treatment with osmic acid, which appears to give little distortion of the tissue elements and gives a good preservation of the blood cells and blood-vessels. The staining method used was Heidenhain's iron-alum hæmatoxylin.

The thyroid glands of normal mice taken at random from the stock show considerable variations, but the gland of normal rats is more uniform, provided that the animals have been carefully kept on a constant diet in a room with a fairly warm and constant temperature, and that intercurrent diseases such as enteritis or bronchopneumonia are not prevalent in the stock. The thyroid gland of a normal rat shows alveoli filled completely with colloid, which, when stained with hæmatoxylin and differentiated with iron alum, does not resist decolorisation. The alveoli are round and have a regular outline. Their size differs in different parts of the gland : a few large distended alveoli are usually situated at the periphery, but the variations are not extreme and very few collapsed or empty alveoli are visible. The lining cells are cubical to columnar. Very few capillaries are visible among the lining cells of the alveoli and those which are visible are small. The mitochondria within the cells are distinct.

By feeding a rat on thyroid gland for four or five days, the gland is relieved of the necessity of secreting the hormone. If in this way the activity of the gland is diminished, no very obvious change is noticed in the thyroid gland. The only difference is that the mitochondria are less distinct and that the colloid resists decolorisation by iron alum, so that it appears darkly stained. The fact that the affinity of the colloid for Heidenhain's hæmatoxylin in material fixed in Schridde's fixative is increased the more of the specific hormone it contains is presumably due to a change in reaction of the colloid. The same conclusion has been reached recently by Hewer as the result of observations on human material in various pathological conditions of the thyroid gland. Plate 16 shows this difference in the appearance of two thyroids: one from a normal, the other from a thyroid-fed rat. The sections had been fixed on the same slide and have thus been stained and decolorised together. Removal of one lobe of the gland has very little effect on the appearance of the remaining lobe. But observations on the effects of changes in the thermal environment reveal corresponding changes in the thyroid gland. The thyroid gland of a rat which has been kept in a hot room at about 30° C. for a day presents an appearance almost identical with that of a thyroid-fed rat: the alveoli are completely filled with deeply staining colloid and lined by cells cubical to columnar in shape. The mitochondria stain only faintly. This is the picture of a resting gland.

When a rat or a mouse is transferred from a warm to a cold environment, or when sympathetic fever is induced, a very profound change is produced in the gland. The most obvious change is an intense congestion. Numerous capillaries open up, which were invisible in the resting gland, not only in the interalveolar spaces, but also among the cells lining the alveoli, or rather between them and the basement membrane surrounding each alveolus; the " intra-alveolar capillaries " as we shall call them for

short. It is only in such a gland that one becomes aware of the enormous vascularity of the gland, a whole network of capillaries being situated between the lining cells of each alveolus and the basement membrane. Such a gland affords perhaps the most striking illustration of the autonomous control of the capillaries to which the work of Krogh has recently drawn attention, especially when one contrasts the capillary congestion in the thyroid gland with the absence of congestion in the parathyroid. As a result of the opening up of the capillaries the lining cells are lifted up, so to speak, from the basement membrane and pushed forward into the lumen of the alveoli, which thus lose their regular outline. Sometimes the dilatation of the capillaries is so great that here and there a lining cell is stretched and only a narrow band of its cytoplasm separates the lumen of the capillaries from the lumen of the alveoli. It is readily seen how a few red blood cells may be driven into the lumen of an alveolus as a result of this capillary distension. Another result is that the lining cells may actually become detached and be found lying free in the lumen of the alveoli. The red blood cells and the detached lining epithelial cells which thus come to lie among the colloid gradually undergo degenerative changes. The colloid itself loses its affinity for the hæmatoxylin stain and is greatly diminished in amount in rats exposed to cold or subjected to sympathetic fever. Many alveoli are completely collapsed and show no colloid at all. The lining cells assume a more columnar shape and the mitochondria are greatly enlarged and more distinct. The changes which we have described may be so intense that the thyroid loses its characteristic microscopic appearance so completely as to make it difficult to identify a section as thyroid-gland tissue. (Plates 18-21.)

When the thermal environment is changed in the opposite direction and rats or mice are exposed to a temperature of 37° C. the alveoli expand and become greatly distended with colloid, which has a great staining affinity

for Heidenhain's hæmatoxylin, the lining cells become smaller, flattened and show only indistinct mitochondria. A diagrammatic representation of these changes is given in Text Figure 2. Our findings that variations in the thermal environment affect the structure of the thyroid have been confirmed by Mills and by Hart. Seasonal variations in the iodine content of the thyroid have been

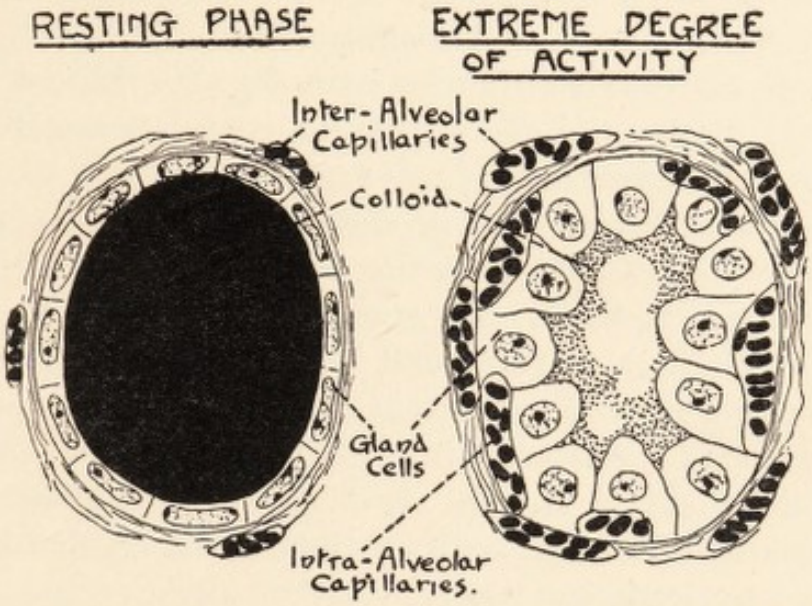

FIG. 2.—Pictographic summary by Dr. R. J. Ludford of the gross histological differences between the alveolus of a resting and an active thyroid gland.

observed repeatedly (Seidell and Fenger, Fenger, Sugata): it is higher in the summer than in winter. Kendall found less thyroxin in winter than in summer.

These observations enable us to interpret extreme changes in the morphological appearance of the thyroid gland in terms of its functional activity. In a resting gland the alveoli are round and contain a homogeneous colloid which fills the alveoli completely and may even distend them. The capillaries underneath the lining cells of the alveoli are mostly closed. The size and shape of the lining cells is not of much significance, for they may vary with the degree of distension: they flatten out with increasing distension, though there may be con-

ditions in which an atrophic condition of the cells occurs independently of the distension. Great functional activity of the gland finds its expression in an irregular outline of the alveoli, in disappearance of the colloid and loss of staining affinity for Heidenhain's hæmatoxylin, in great congestion of the gland and particularly in the opening up of the capillaries underneath the lining cells, in desquamation of the lining cells and in small hæmorrhages into the lumen of the alveoli. In dealing with the human thyroid gland we shall see that human pathology furnishes appearances of the thyroid gland giving a complete counterpart of these two conditions of rest and activity. In this connexion it is interesting to note that according to de Quervain such a change in the human thyroid occurs at the moment of birth. He states " the thyroid gland of the new-born is characterised by an absence of colloid, desquamation of the epithelial cells and a marked development of the vascularity ". He gives no explanation for this change. In the light of our observations it explains itself as the result of the sudden change in the thermal environment which occurs at birth.

The study of the thyroid at rest and in activity suggests also an explanation of the mechanism by which the passage of the specific thyroid hormone from the interior of the alveoli into the blood-stream may be brought about. How the colloid, which is an inanimate viscous fluid and which in the resting gland lies in an enclosed space in the lumen, is made to pass into the blood-stream is rather a unique problem of secretion. For its solution our observations offer the following suggestion. If rats or mice are exposed first to a hot environment, so that the alveoli get distended with colloid, and then exposed to a cool environment, one can sometimes see in glands fixed during the process of disappearance of the colloid from the alveoli, a narrow cleft between two adjacent cells of one alveolus. This cleft is filled with darkly staining colloid, which abuts against one of the distended intra-

alveolar capillaries (see Plate 22). When the intra-alveolar capillaries open up, as they do if the gland is stimulated to activity, the pressure on the colloid in each alveolus must increase greatly, as the cells are being pushed up against it. This also puts a strain on the cells lining the alveoli, so that at one point they may get pushed away from each other and the resulting cleft forms an outlet for the colloid. This is not necessarily the only way in which the colloid disappears from the centre of the alveolus, but it is at any rate one process capable of demonstration.

We may point out in passing that a similar mechanism may be concerned in establishing the flow of milk from the mammary gland. Experimentally, a very sudden and copious flow of milk from the ducts can be induced by the injection of pituitrin. Pituitrin does not stimulate the actual formation of milk ; it only makes the milk flow out which has accumulated in the alveoli. It also produces intense congestion of the gland. The normal stimulus of suckling also produces a vascular dilatation. It is readily seen how such a dilatation in the close network of capillaries which invest the alveoli of the gland would tend to compress the alveoli and thus squeeze the milk out into the ducts.

In the mouse it is more difficult to get homogeneous pictures of the resting thyroid gland than in the rat. The thyroids of normal mice kept at ordinary room temperature show much greater inequality between the size of the alveoli, the amount and the staining reaction of the colloid and the degree of capillary dilatation. In other words, the glands of normal mice kept at ordinary room temperature (16°-18° C.) always show a considerable degree of functional activity, so that the effect of exposure to cold is not so striking as in the rat. This is readily understood if we remember that the mouse is a much smaller animal than the rat, and that it has not only a very small mass of living tissue which can produce

heat, but also a relatively large surface (in proportion to its mass) which dissipates heat. The effect of heat, on the other hand, is even more striking in the thyroid of the mouse as shown in Text Figures 3, 4 and 5. In mice which have been kept at 35° C. for six hours the thyroid shows a uniform appearance of resting alveoli distended with colloid which stains deeply with hæmatoxylin. As in the rat, a resting condition of the gland can be induced in mice by thyroid feeding, as well as by a change from a

FIG. 3.—Thyroid gland of mouse kept at room temperature.

cold to a hot environment. An extreme condition of the gland was obtained in an experiment in which mice were fed for three months with such small doses of thyroid gland that they did not lose in weight. The appearance of such a gland is represented in Plate 17, and shows an almost goitrous condition of the gland.

We have already referred to the fact that the staining of the mitochondria becomes less distinct in the gland in which thyroid feeding has induced a complete rest. The relationship between the activity of a cell and changes in its internal structure is one of the fundamental problems

of cytology, and has, especially in recent years, been studied repeatedly in gland cells, especially with reference to the mitochondria and the Golgi apparatus. A study of these cytological structures in the cells of the resting thyroid gland, *i.e.* after heat and thyroid feeding, and in the actively secreting gland after cold and in sympathetic

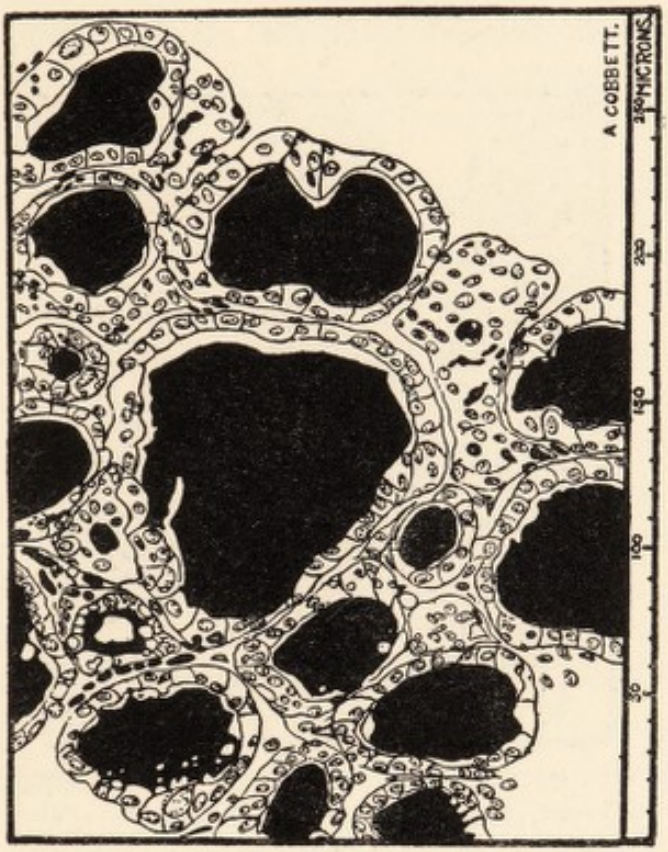

FIG. 4.—Thyroid gland of mouse six hours after change from a cold to a hot environment (35° C.).

fever was undertaken in collaboration with Dr. R. J. Ludford. It was found that the internal cell structure of the thyroid cells undergoes profound changes when the gland is stimulated to increased activity. The most striking change is in the mitochondria, which undergo an enormous enlargement in the active cell, especially so after the injection of T.H.N. The Golgi apparatus also enlarges in the active cell and then breaks up. These changes have been described and figured in a separate

paper, so that it is not necessary to deal with them here in detail. It is sufficient to state that these observations on the finer cytological changes in the cells of the thyroid during activity of the gland confirm the conclusions based on the disappearance of the colloid and capillary dilatation.

According to Bensley the mitochondria of the thyroid cells are often densest near the alveolar lumen next to

FIG. 5.—Thyroid gland of mouse six hours after change from a hot environment (35° C.) to a cold environment (5-10° C.).

(Figs. 3-5 reprinted by permission of the Cambridge University Press from the *Journal of Physiology*.)

the colloid. Since in the kidney cells they are densest near the peripheral blood-vessels, he speaks of the polarity of the thyroid cells being reversed and looks upon the position of the mitochondria as indicating the direction of secretion. It is doubtful, however, whether the mitochondria of a gland cell always indicate the direction in which secretion occurs. In the acinar cells of the pancreas, for instance, the mitochondria are found lying mostly in the peripheral portion of the cell away from the zymogen granules. The Golgi apparatus is a more reliable in-

dicator of cell polarity with reference to secretion. Recent work on the Golgi apparatus has yielded abundant evidence that the specific secretion of a gland cell is formed in intimate relationship to the Golgi apparatus. In all resting gland cells this cytoplasmic structure is small and contracted, and lies on that side of the nucleus which is directed towards the secreting surface of the cell. If the cell begins to secrete the Golgi apparatus enlarges, spreads out from the nucleus towards the secreting surface and eventually breaks up, to reconstitute itself again during rest. This relationship of the Golgi apparatus has been found to hold good for the cells of all externally secreting glands in which it has been investigated. In the resting thyroid gland the Golgi apparatus is found on the side of the nucleus directed towards the alveolar lumen. This is again in accord with the view that the Golgi apparatus indicates the direction of secretion. In the various conditions of extreme activity of the gland, such as exposure to cold and sympathetic fever, the Golgi apparatus enlarges but retains the same position between nucleus and alveolar lumen. It might have been thought that in the active gland the cells secrete their specific hormone directly into the capillaries. But if the position of the Golgi apparatus can be accepted as a reliable indicator of the direction of secretion, one must conclude that even in the very active gland the secretion is poured first into the alveolar lumen and passes from there into the bloodstream. Cowdry has described and figured cells from the thyroid gland of a guinea-pig in which the position of the Golgi apparatus was reversed, and he has interpreted this change as indicating that in those cells the direction of secretion was reversed. The change seems to have been observed accidentally in the gland of an apparently normal animal, so that no data are available to indicate whether the particular thyroid gland was exceptionally active. Since in our material we have been able to vary the degree of activity of the gland at will we have looked carefully

for the occurrence of such a reversal. But, as already stated, we have never been able to observe it in the cells of a normal gland.

The examination of the gland of a mouse suffering from exophthalmic goitre has, however, shown this phenomenon in a very striking manner. We are greatly indebted to Professor Leonard Hill for placing this unique material, which will be described in detail in a separate paper, at our disposal. In this gland many of the cells show an enormously enlarged Golgi apparatus situated between the nucleus and the intra-alveolar capillaries, indicating a direct secretion of the thyroid hormone into the capillaries. Further observations on human material from Graves' disease are necessary to determine whether this reversal of polarity is a constant feature of the disease. It is obvious that a direct secretion of the thyroid hormone from the cells directly into the blood-stream is not subject to the same control as the normal process in which the hormone is first secreted into the alveolar lumen and then passed from there into the blood-stream. If, therefore, the occurrence of a change in polarity can be established in Graves' disease it might in itself offer an explanation of the disease.

To return now to the functions of the normal gland :

It will be seen that the two conditions—exposure to cold and sympathetic fever—which induce in addition to disappearance of the colloid a profound morphological change in the thyroid gland, indicating an increased functional activity of the gland—are also those conditions which stimulate the adrenal gland to increased functional activity. Both these conditions are associated with increased heat production. Conversely, exposure to heat diminishes the secretion of the thyroid hormone into the blood-stream, so that the colloid accumulates in the alveoli. We shall see later that heat also inhibits the activity of the adrenal gland. These observations offer an explanation for the great seasonal variations in the

amount of the thyroid hormone present in the gland, which, as already stated, was found to be much less in winter than in summer. The changes which we have described offer direct evidence of the close relation of the thyroid gland to the regulation of the body temperature. In addition there is the following indirect evidence. Thyroid feeding produces a distinct rise of temperature

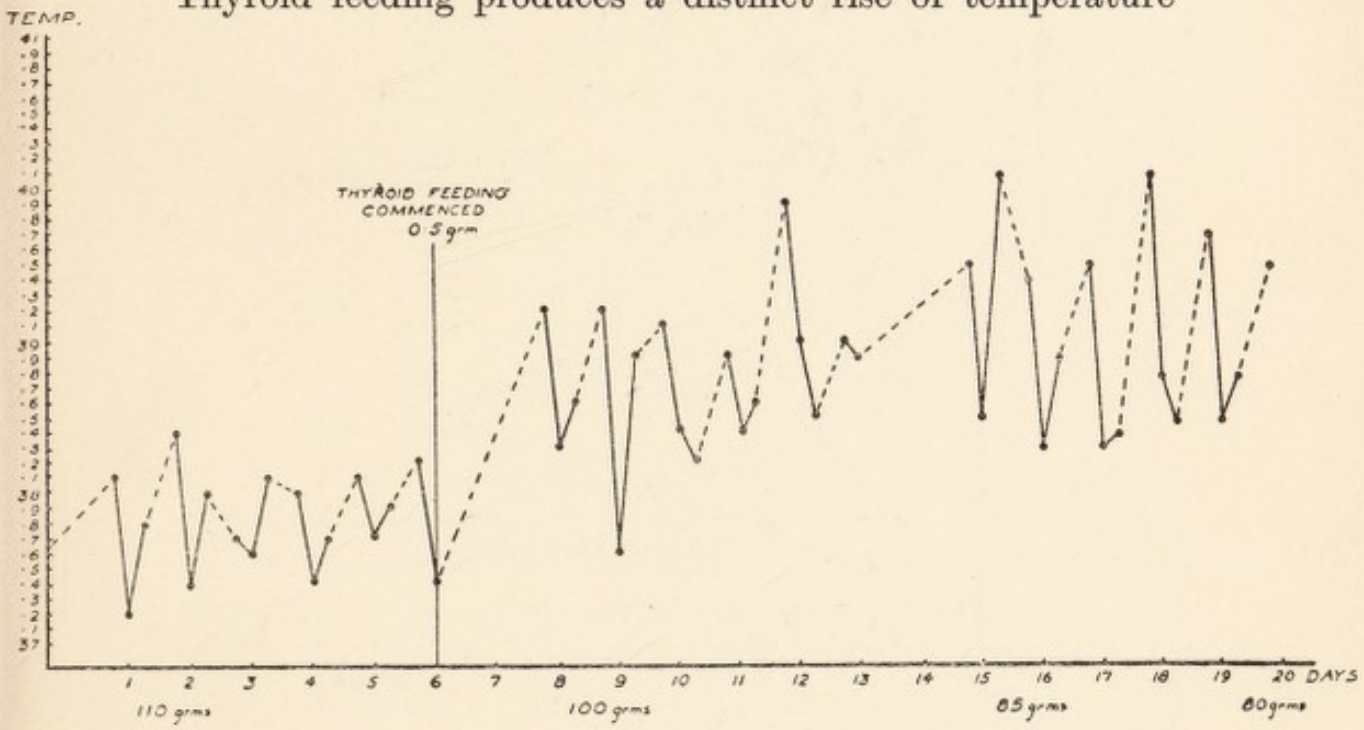

FIG. 6.—Temperature curve of rat before and after thyroid feeding. The temperature was taken three times a day—at 10 A.M., 1 P.M. and 5 P.M. Note that thyroid feeding produces not only a rise in temperature but also a hectic type of fever.

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of the hectic type, as the accompanying chart shows (Text Figure 6). This effect of experimental hyperthyroidism finds its counterpart in the raised temperatures frequently observed in cases of Graves' disease. Again in thyroid-fed animals fever is induced more readily by β-tetrahydronaphthylamine than in normal animals, while conversely thyroidectomised animals respond less actively to this substance. The same difference can be observed if fever is induced by injection of *B. typhosus* vaccine. These state-

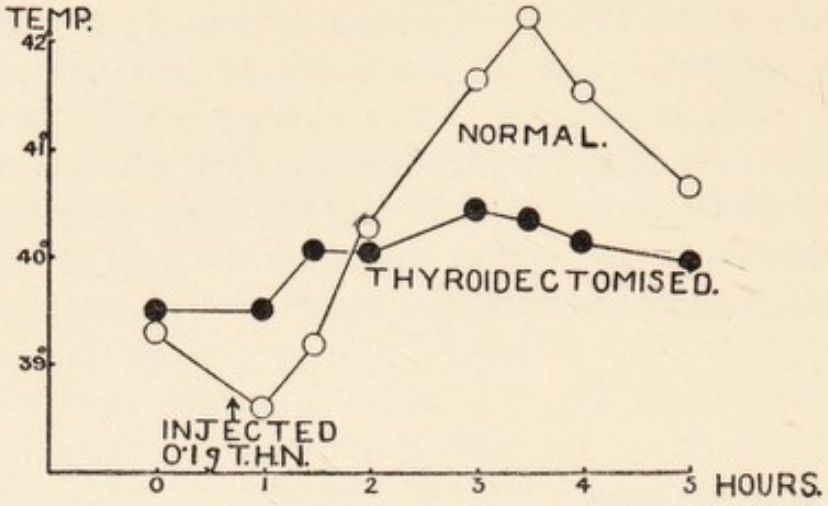

Fig. 7.

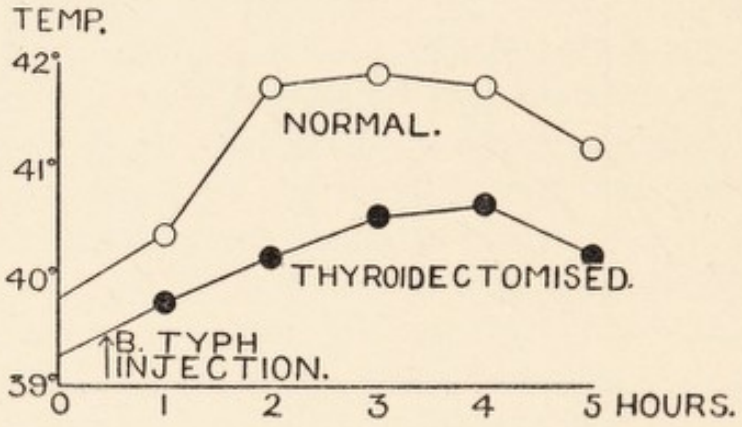

Fig. 8.

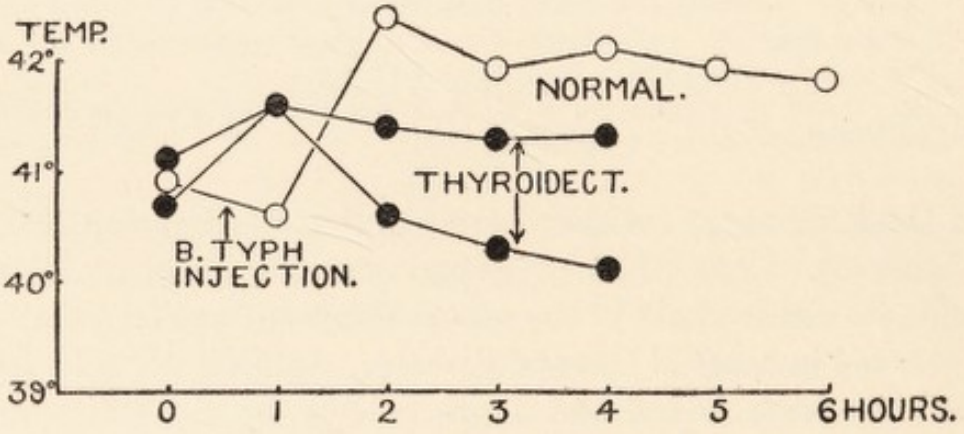

Fig. 9.

ments are illustrated in the accompanying charts (Text Figures 7, 8 and 9).

These results are in agreement with a recent observation of Evans and Zeckwer, who found that the hyperglycæmia induced in rabbits by the injection of *B. proteus* vaccine failed to appear in a thyroidectomised animal, but reappeared after thyroid feeding.

Summary.

In this chapter the relation of the thyroid gland to the heat regulation of the body is demonstrated by the following observations.

Exposure to cold and injection of the pyrogenic substance β-tetrahydronaphthylamine stimulate the gland to intense functional activity, exposure to heat inhibits it. These effects are the same as those observed in the adrenal gland, so that the conditions which stimulate one gland also excite the other.

In experimental hyperthyroidism the temperature is raised and the organism is more sensitive to the pyrogenic action of β-tetrahydronaphthylamine. After thyroidectomy the organism becomes less sensitive to this action.

Further evidence recorded in the literature concerning the relation of the thyroid gland to heat regulation has been discussed in the first chapter.

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CHAPTER V

THE THYROID AND ADRENAL GLANDS AS ENDOCRINE FACTORS IN THE CONTROL OF METABOLISM AND OF HEAT REGULATION

THAT the thyroid gland through its internal secretion exercises a profound effect on metabolism is one of the most securely established facts of endocrinology. The experimental hyperthyroidism produced by thyroid feeding and the pathological hyperthyroidism represented by Graves' disease agree in showing that an increased secretion of the thyroid hormone raises the basal metabolism, increases the oxidation of fats, increases the nitrogen excretion in the urine (thus indicating an increased protein destruction) and increases the heat production. Although these facts are so well established that the basal metabolism is now taken clinically as a guide in the diagnosis and treatment of thyroid disorders, the manner in which these metabolic effects are brought about by the thyroid hormone was not understood until it was found that there is also a stimulation of the glycogenic function of the liver : the liver forms more carbohydrate from protein and fat and passes into the blood more carbohydrate which is then oxidised.

It will be discussed more fully in the following chapter that the term " glycogenic function " of the liver is used by us in a sense different from that commonly used. The current view sees in the glycogenic function merely the storage of glycogen so that the amount of glycogen present in the liver at a given moment is taken as the measure of

the glycogenic function. This is a static conception which, in our opinion, is erroneous. In our view, which is a restatement of the original conception put forward by Claude Bernard, the glycogenic function must be considered dynamically, like any other secretory function of a gland cell, as the rate at which carbohydrate is *formed* by the liver cells *and secreted* by them into the bloodstream in the form of glucose. On this view the amount of glycogen present in the liver cells at any given moment represents merely the balance between the rate at which it is formed and that at which it is secreted, and does not have, therefore, the significance, which is given to it in the static conception of a reserve or a store. To describe this function succinctly Claude Bernard coined the term " internal secretion ", and applied it to the liver glycogen. For the purpose of following the argument developed in this chapter the reader is asked to accept this definition and to refer to the following chapter and to one of our published papers for a detailed discussion of this important problem.

The work of Lusk on the effect of an increased intake of glucose has shown that an increased supply of glucose to the cells leads to an increased oxidation, " the metabolism of plethora ", as he calls it. Similarly the stimulation of the glycogenic function of the liver induces an increased pouring of glucose into the blood and thus leads to an increased oxidation of carbohydrates, not to a glycosuria, as was formerly supposed. If the stimulating effect of the thyroid hormone on the liver is maintained sufficiently long—over several days—glycogen gradually disappears from the liver, because the rate at which it is poured into the blood in the form of glucose is as great as the rate at which it can be formed. The liver thus becomes practically free from glycogen, even though the animal may receive a diet rich in carbohydrates, and may remain so for days or a few weeks if the action of the thyroid continues. It has been shown that this absence

of glycogen is not due to an inability of the liver cells to form glycogen, but is the result of an increased activity of the liver cells, which are forming carbohydrate more actively than normally from proteins and fats and are also passing it into the blood at a greater rate than normal. This increased formation of carbohydrate from proteins and fats finds its expression in the gradual lowering of the respiratory quotient in experimental hyperthyroidism, when short periods immediately after a meal rich in carbohydrates are being examined. The increased glycogenic function is responsible for the increased destruction of proteins and fats in hyperthyroidism and for the increased nitrogen excretion in the urine. The increased pouring of glucose into the blood from the liver results in a metabolism of plethora which in itself leads to an increased heat production. To this we have to add the effects of general sympathetic stimulation, which increases the heat production by increasing cellular activity.

We have already stated that the effect of thyroid feeding in man presents clear evidence that the thyroid hormone excites the sympathetic. Tachycardia, flushing of the skin with perspiration, even tremor of the hands and exophthalmus have been observed in man after thyroid feeding. This increased activity of muscular tissues (tachycardia, tremor, etc.) resulting from sympathetic stimulation is, of course, also a factor increasing heat production. It is possible, therefore, to explain the condition of increased metabolism in hyperthyroidism as resulting from the stimulating action of the thyroid hormone, both on the glycogenic function of the liver and on the sympathetic nervous system. And since the glycogenic function of the liver is itself under the control of the sympathetic, it is probable that the effect of the thyroid hormone on the glycogenic function must also be interpreted as a stimulation of the sympathetic.

The action of the thyroid hormone is slight, slow but lasting; there is, in fact, a definite cumulative action.

Thus Kendall has shown that one large dose of thyroxin produces no ill effects, while the same amount administered in small daily doses produces all the symptoms of hyperthyroidism and death. The action of adrenalin, on the other hand, is rapid, strong but very transient. As a result immediate effects, which can be recorded, such as effects on blood pressure, intestinal movements, etc., are very conspicuous and have been studied in great detail, while the effects on metabolism induced by an injection of adrenalin pass off so rapidly, especially if doses within physiological limits are used, that they are difficult to detect. Hence little importance was attached to the adrenals as an endocrine factor controlling metabolism. Until recently our knowledge was limited to the disappearance of glycogen from the liver, an increase of sugar in the blood and the occasional appearance of sugar in the urine after such massive doses of adrenalin that they probably exceed by a large margin the amount which can be secreted by the active gland in an intact animal. In any case adrenalin glycosuria has no relation to the glycosuria of diabetes mellitus, since it is not associated with an inability of the tissues to burn sugar. It may quite well be the result of the renal anæmia, induced by large doses of adrenalin, making the renal epithelium for a time more permeable to glucose and thus more sensitive to the hyperglycæmia induced by adrenalin. In view of the transient nature of the effect produced by injecting single doses of adrenalin it was necessary to induce a prolonged adrenalinæmia, if one wished to demonstrate the effects of an increased activity of the adrenal glands on metabolism. The ideal method is obviously to induce a physiological adrenalinæmia by stimulating the adrenal medulla to prolonged secretion. The use of anæsthetics, which by themselves affect both metabolism and the activity of the adrenal, was necessarily excluded. The search for suitable stimuli of adrenal secretion led to the finding that exposure to cold was a strong stimulus for

the gland. The production of fever by the injection of β-tetrahydronaphthylamine is another condition involving an active secretion of adrenalin. Both conditions have in common that the heat production is greatly increased, glycogen disappears from the liver, the blood sugar rises and the oxidation of carbohydrates is increased. In the sympathetic fever induced by β-tetrahydronaphthylamine observations are on record showing, in addition to the changes just enumerated, an increased nitrogen excretion in the urine as a late phenomenon. The importance of the adrenal gland as a powerful factor influencing and controlling the general metabolism thus became evident. The effects of this drug are those of a prolonged adrenalinæmia, both as regards the circulation and metabolism.

These metabolic changes are in fact qualitatively the same as those produced by hyperthyroidism, only they are more acute and more rapid than those produced by thyroid feeding. But they are related to each other in the same way. In both conditions we have a greatly increased heat production, a disappearance of glycogen from the liver, a rise in the blood sugar without glycosuria, an increased nitrogen excretion. The primary effect is the increased activity of the glycogenic function which through increased secretion of glucose into the blood leads to a " metabolism of plethora ", while through increased formation of carbohydrate from protein it increases the nitrogen excretion in the urine. The increased heat production is the result of increased muscular activity (tachycardia, rapid respiration, muscular tremor) for which the increased secretion of glucose from the liver provides at once increased fuel. Since the metabolic changes induced by an adrenalinæmia are brought about by the stimulation of the sympathetic, it may be concluded that the same changes when induced by thyroid feeding are brought about in the same way. The experimental evidence does not yet indicate clearly whether the action of the thyroid hormone is due to a direct stimulating

effect on the sympathetic, or to a stimulating effect on the adrenal glands, or, thirdly, whether it renders the sympathetic nerve endings more sensitive to adrenalin. Observations on the effect of thyroid feeding in Addison's disease might give valuable information on this point.

Boothby and Sandiford have confirmed this effect of adrenalin on metabolism. They showed that the injection of even a single dose of adrenalin produces a measurable increase in heat production. They called this effect at first the " specific dynamic action " of adrenalin and later altered this term to the " calorigenic action " of adrenalin. It is, however, quite unnecessary to invent a new name or to postulate a new specific property for this effect of adrenalin, since, as we have seen, it readily explains itself as the result of a well-known effect of adrenalin, namely, sympathetic stimulation. McIver and Bright have demonstrated recently an increase in metabolism as the result of stimulating the adrenals to increased secretion, while, conversely, removal of the adrenals was followed by a fall in metabolism.

It has been stated repeatedly, though erroneously, that the thyroid hormone stimulates directly the metabolic processes of all the cells. No evidence has ever been produced that it does so and it is not explained how it might do so. Sometimes an attempt at an explanation is made by some such analogy as that " the thyroid acts like a bellows on the metabolic fires ". But this analogy is a false one. It was devised when the mechanism by which this stimulating action was produced was not understood. If we are to use such an analogy we ought to liken the action of the thyroid hormone, and incidentally that of adrenalin, to throwing fresh fuel on the metabolic fires. If the metabolic fires are burning well, as they do in a normal organism, this would make them burn more brightly. But if they are burning badly, as they do, for instance, in diabetes mellitus, the addition of fresh fuel would make the fires smoke or might even extinguish

them ; in terms of physiology it should increase the glycosuria. If, on the other hand, the action of the thyroid were really comparable to that of a bellows it should make the fires burn more brightly in diabetes, and thyroid gland should be of therapeutic value in that condition. What happens actually, when thyroid gland is administered to a diabetic patient, is that the condition is aggravated. A similar harmful effect may result from exposure to cold, which, as we have seen, stimulates the thyroid and adrenal glands to increased activity. Conversely, removal of the thyroid gland in experimental pancreas diabetes greatly diminishes the excretion of sugar and may even make it disappear (see Chapter VI.).

The throwing on of fresh fuel is, however, only one result of the increased activity of the thyroid and adrenal glands. The other does not find a counterpart in the analogy. We would have to extend it by saying that the heat generated by the metabolic fires is used to drive an engine. When the body is at rest this engine runs with a minimal load. When the cells are stimulated to activity, as they are by increased activity of the thyroid and adrenal glands, the load is increased. The thyroid-adrenal apparatus is thus a mechanism which ensures automatically an increased supply of fuel to those cells and organs which it can stimulate to an increased activity.

We have so far followed the effects of increased functional activity of the thyroid and adrenal glands on metabolism, and found that in both cases there is an increased heat production and that the increased supply of fuel is brought about by stimulation of the glycogenic function of the liver.

We may now start from the other end, so to speak, and consider the mechanism of heat regulation in a mammal.

In the heat regulation of the warm-blooded organism two mechanisms are distinguished : the physical heat regulation is concerned with variations in the heat loss, the chemical heat regulation is concerned with variations

in the heat production. The organs mainly concerned with the physical heat regulation are the respiratory tract, the cutaneous blood-vessels, and in man and in some animals, such as the horse, the sweat glands. Freund (1920) has recorded an interesting observation bearing on this point. Adrenalin, if applied to the hand by kataphoresis, produces a sharply defined anæmic area. If now the hand is placed in a hot-air apparatus the anæmic region begins to sweat earlier and more intensely than the other parts of the hand. In most animals the sweat glands are restricted to a small area, such as the pads of the feet, and are not therefore of functional importance in the physical heat regulation. Their function is then subserved, although not as efficiently, by the hairs of the fur: activity of the sweat glands, which increases heat loss, corresponds to erection of the hairs of the fur which fulfils the same purpose. Both the sweat glands and the arrectores pilorum muscles are innervated by the sympathetic which also controls the lumen of the cutaneous blood-vessels. The normal condition of the skin is, in fact, dependent on the normal functioning of the thyroid and adrenal glands, and there is a considerable body of clinical evidence to show that diseases of these glands are followed by pathological changes in the skin. The respiratory mechanism, which also takes a part in the physical heat regulation through the vaporisation of water in the lungs, is also affected by adrenalin. Adrenalin, even in moderate doses, affects the respiration in an unanæsthetised animal. This fact does not seem to be known. Indeed, it is stated in all text-books and illustrated by tracings that adrenalin apart from a transient apnœa has no marked effect on respiration. This is quite correct when observations are made on anæsthetised animals. Even then the doses of adrenalin necessary to produce the apnœa are so enormous as to make it impossible for this apnœa ever to occur under physiological conditions. But in unanæsthetised rabbits even small doses of adren-

alin, which are ineffective in the anæsthetised animal, will produce a considerable alteration of the pulmonary ventilation. And if a lasting adrenalinæmia is induced in animals by a dose of T.H.N. they show rapid, panting, vigorous breathing. This effect on the respiration may be an indirect one due to the pulmonary congestion induced by adrenalin. It is well known that the pulmonary blood-vessels do not share in the general constriction of the arterioles resulting from sympathetic stimulation, so that the lungs get intensely congested. With very large doses of adrenalin this may go so far as to lead to pulmonary hæmorrhages from which the animal dies.

All the factors concerned in the mechanism of physical heat regulation are therefore controlled by the sympathetic nervous system. Its stimulation diminishes heat loss in so far as it constricts the peripheral blood-vessels, it increases heat loss in so far as it affects the pulmonary ventilation and raises the hairs of the fur or produces sweating. It must be remembered, however, that intense cutaneous vaso-constriction inhibits the activity of the sweat glands, so that in man and in certain animals which regulate by means of sweat glands an intense stimulation of the sympathetic affects the physical heat regulation mainly in one direction, namely, that of diminished heat loss. In most of the laboratory animals the heat-regulating function of the sweat glands is replaced by that of the arrectores pilorum which are not inhibited by cutaneous vaso-constriction. The significance of this difference in the heat regulation of different species will be referred to again later.

The chemical heat regulation may be defined with Rubner as the process by which the organism increases its heat production above the level of the basal metabolism. When the organism is completely at rest its metabolism reaches a certain minimal level at a certain temperature of the surrounding air. Under these conditions only the processes necessary in maintaining the life of the

organism are proceeding, and these cannot be reduced further, so that the production of heat resulting from these processes cannot be reduced below this minimal level. The heat production can, however, be greatly increased by an increased oxidation. We know that the carbohydrates are the organic material mainly used when there is a demand for increased heat production and that the muscles are the main tissues in which this increased oxidation is carried out. The natural reaction to exposure to cold is voluntary muscular movement. If this is suppressed, "shivering" takes its place which is involuntary muscular movement. In the increased heat production of fever we may meet with this same involuntary muscular movement of shivering in the rigor accompanying some acute bacterial infections. The increased flow of carbohydrate to the tissues, when heat production is increased either as the result of exposure to cold or in fever, is illustrated most strikingly by two facts: the glycogen disappears from the liver and the blood sugar increases. (For hyperglycæmia after cooling, see Geiger, 1925; for hyperglycæmia in bacterial infections, see Labbé and Boulin, Berg, Zeckwer and Goodell, Evans and Zeckwer; see also Chapter VIII.) In this connexion it is interesting to note that Orbeli has recently adduced experimental evidence which demonstrates a sympathetic innervation of skeletal muscle similar in effect to that of heart muscle. The influence of the sympathetic system upon the activity of skeletal muscle corresponds in Orbeli's view with Pawlow's conception of trophic innervation, that is, an innervation which governs the chemical activity underlying muscular contraction and the metabolic exchange involved. According to Orbeli all the vital activities of muscle are stimulated by sympathetic stimulation, a conclusion which is in harmony with our conception of the sympathetic system as controlling the heat regulation of the body. A somewhat different view has been propounded by Hunter and

Royle, who hold that the tonus of muscle is dependent on sympathetic supply. This view has, however, been questioned by other workers (for discussion see Evans). Our observations afford some circumstantial evidence on the relation of the sympathetic to muscular movement. An involuntary muscular tremor occurs in a number of very different conditions : the tremor of Graves' disease, the shivering of cold, the rigor of a fever, the shivering of fear. All these have in common a greatly increased activity of the thyroid adrenal apparatus and therefore of the sympathetic.

We see, therefore, that all the mechanisms concerned in the physical and chemical heat regulation are directly or indirectly affected by the sympathetic and can be set in motion by the activity of the thyroid and adrenal glands. Thus, when we stimulate the adrenals to a lasting massive secretion of adrenalin as, for instance, by the injection of T.H.N., the result must be increased heat production and diminished heat loss, *i.e.* fever. When we expose a warm-blooded animal to cold there is an increased activity of the thyroid and adrenal glands which increase heat production and diminish heat loss and thus enable it to maintain its temperature. The thyroid and adrenal glands are therefore endocrine factors of heat regulation. It is not necessary to postulate for their hormones any hypothetical calorigenic action, apart from their known action on the sympathetic nervous system. It is in fact an essential part of this conception, that the intrinsic mechanism of heat regulation is a function of the sympathetic nervous system. The secretion of the thyroid and adrenal hormones reinforces and prolongs the action of the nervous system. Griffith has shown that stimuli which raise the blood sugar in normal animals have a less strong effect when the adrenals are excluded, while stimuli which may be too weak to cause by themselves a pronounced mobilisation of carbohydrates may be effective if they have the sustained

co-operation of the reflex by stimulated adrenalinæmia. This disposes of much of the controversial literature that has accumulated on the question whether the adrenals do or do not participate in such experimental conditions as sugar puncture or heat puncture. This duplication of the effects of a nervous stimulation by the results of endocrine activity is the outstanding feature of the general action of adrenalin. The activity of the adrenal itself, innervated as it is by the sympathetic, is subject to stimulation by the action of adrenalin, although, as we shall see, in that case a reverse inhibitory effect comes into play. The result of such dual control of heat regulation is that the effect of nervous stimulation is reinforced and prolonged. The endocrine apparatus acts as a sort of relay by which a short and comparatively weak stimulus passing along the sympathetic is prolonged and reinforced by inducing the secretion of the thyroid and adrenal hormones. A good illustration is the tonic stimulating effect of a cold bath which lasts long after the stimulus of cold has ceased to act.

Another illustration of a more scientific nature is offered by some observations recorded by Graham Lusk in his fundamental work on animal calorimetry. He found that more heat was produced when a solution of glucose in cold water at 18° C. was drunk than when it was given in water at 38° C. Even cold water by itself at 18° C. gave an increased heat production in one experiment. The surprising fact is that this increased heat production should reach its maximum as late as three hours after the water was given, for during the first hour the water must have been absorbed, or at least if not absorbed, would have been warmed to the body temperature. After the first hour there cannot have been any nervous stimulation resulting from the contact of water below the temperature of the body with the walls of the stomach. The effect was so unexpected that Lusk's comment may be given here: "A decided feeling of

chagrin must be admitted by the writer in acknowledging that during a period of four years he had wrongly assumed that the ingestion of material regardless of its temperature would be equalised in the body during a preliminary period of three-quarters of an hour and would exert no influence upon the results". It is indeed difficult to believe that this prolonged effect can be due directly to the short nervous stimulus induced by the introduction of cold water. But it readily explains itself as the effect of the endocrine apparatus which has been set in motion by the nervous stimulus. Indeed, since writing this, Cannon and his collaborators have used the introduction of cold water into the stomach as a method of demonstrating the secretion of adrenalin in response to the stimulus of cold.

As we should expect on the basis of this conception the heat regulation is impaired but not destroyed when the ancillary endocrine apparatus is eliminated by disease as in myxœdema and Addison's disease, or when it is removed experimentally (Belding and Wyman). Conversely, one would expect the heat regulation to be destroyed by lesions which eliminate all sympathetic control. This, in fact, is the case. The work of Freund and his collaborators, Isenschmid and Krehl, Karplus and Kreidl, Leschke and others on the effect of various nervous lesions on heat regulation may be summarised as showing that the power of heat regulation is impaired progressively, as the lesions involve more and more of the sympathetic nervous system. In cases of tumour of the cervical cord disturbances of heat regulation (hyperthermia or hypothermia) have been noted occasionally (Abrahamson and Grossman).

If the spinal cord is cut at different levels it is found that there is a sharp dividing line when we consider the effects produced on heat regulation. This line lies between the eighth cervical and the first thoracic segment. Sections above that line, that is to say, anywhere through the cervical cord, are followed by complete destruction of

heat regulation. Sections below that line produce only a partial impairment of heat regulation. This is due to the partial paralysis of the vasomotor and pilomotor apparatus and of sweat secretion, and the extent of the paralysis depends, of course, upon the level of the section. This partial impairment by a section high up in the thoracic region can be transferred into a complete destruction of heat regulation if, in addition, the stellate ganglia are extirpated or the cervical roots are cut, although this latter operation by itself does not destroy the heat regulation. All the nervous paths concerned with heat regulation converge in the brain in the subthalamic region in the tuber cinereum, since a small lesion here produces complete destruction of heat regulation. It should be noted, however, that even the most completely destructive lesion does not render an animal, such as the rabbit, completely poikilothermic. If the thermal environment is kept at about 28° C. such an animal can still maintain its normal body temperature at about 38° C. This fact in itself indicates the existence of a heat-regulating mechanism ancillary to the nervous apparatus.

The tuber cinereum may therefore be called the site of the so-called heat-regulating centre. Its position in the hypothalamic region is again evidence of its intimate relation to the sympathetic since electrical stimulation of that region produces the effects of sympathetic stimulation on eye, bladder and uterus.

In speaking of a heat-regulating centre it should, however, be clearly understood that the term is used merely as a physiological connotation of an anatomical structure, namely a collection of nerve-cells which are connected, directly or indirectly, with the sympathetic fibres controlling the blood-vessels, the sweat glands, the pilomotor muscles, the liver, thyroid and adrenal and possibly other endocrine glands connected with heat regulation. The idea which has hitherto dominated all conceptions of heat regulation is that there is a centre which acts as a thermo-

stat. This is vitalism at its crudest. It has led to the even cruder notions that there is not only a "heat centre" but also a "cooling" centre, and further that fever is caused by the centre being "set at a higher level". How far this conception has gone to invert the relation between cause and effect is perhaps best illustrated by the statement, made in a recent paper dealing with the metabolism of fever, to the effect that the increased metabolism in fever is not the cause but the result of the hyperthermia and is a manifestation of the well-known van't Hoff's law which correlates the rate of increase in chemical reactions with increase in temperature. This is putting a vitalistic cart before a mechanistic horse.

Summary.

It will be convenient here to summarise at this point the considerations which have been discussed so far. One of the main functions of the sympathetic concerns the heat regulation of the body, since all the main functional mechanisms which control the heat regulation of the body are innervated by the sympathetic. For the physical heat regulation this holds good for the calibre of the peripheral blood-vessels, the sweat glands and the arrectores pilorum, while respiration is affected indirectly by sympathetic activity. The fuel necessary for increased heat production is provided by the glycogenic function of the liver, so that the chemical heat regulation is also under sympathetic control. All these factors are also affected by the adrenal and thyroid hormones. The increased activity of these glands leads to increased heat production and diminished heat loss, *i.e.* fever. Experimental hyperthyroidism and experimental hyperadrenalinism produce two different types of fever; the first one elicits a hectic type of fever, the second one a rapid hyperpyrexia. Exposure to cold which calls for increased heat production and diminished heat loss is a powerful stimulus of these two glands.

We shall show in subsequent chapters that exposure to heat also produces very distinct changes in the adrenal and thyroid gland, but that these changes are in an opposite direction to those produced by cold, and, further, that in many of the fevers accompanying bacterial infections a stimulation of the thyroid and adrenal glands is involved. From whatever angle the problem of heat regulation is approached, one is always led to the conclusion that the thyroid and adrenal glands represent an endocrine apparatus for the heat regulation of the body.

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CHAPTER VI

THE GLYCOGENIC FUNCTION OF THE LIVER

In the preceding chapter the glycogenic function of the liver was defined as " the internal secretion " of the liver. The current view of the glycogenic function of the liver is that it represents the *storage* of the excess of carbohydrate ingested. The distinction between these two conceptions, which we will call for short the " secretory conception " and the " storage conception ", is not merely a verbal quibble. It is a fundamental distinction which involves the most important aspects of carbo-hydrate metabolism, including its control by the endocrine organs and their relationship to one another. It is of special importance for the subject of this treatise, because the chemical heat regulation of the body—by which is meant the mechanism which provides for an adequate supply of chemical fuel to maintain the body temperature—finds an explanation in the glycogenic function of the liver if we regard this function as a secretory function. So long as we regard the liver glycogen merely as a store or as a reserve of carbohydrate, as it always is described, we can obviously not attribute to it any essential part in the chemical heat regulation. For a warm-blooded animal does not cease to maintain its temperature when the liver is emptied of glycogen, so that there would have to be, on the storage view of hepatic glycogen, some other mechanism which provides the chemical fuel when the glycogen reserve is exhausted. But what this mechanism is has never been demonstrated, and, therefore, the chemical

heat regulation has remained without explanation. We meet with similar difficulties if we try to explain on the basis of the storage conception such aspects of carbohydrate metabolism as the action of insulin or of the thyroid hormone, the interrelationship of endocrine organs, or the disappearance of glycogen from the liver in two such different conditions as pancreas diabetes and experimental hyperthyroidism. In the consideration of these various problems one begins with experimentally established facts on which there is general agreement, but one arrives at diametrically opposed conclusions whether one argues on the storage conception or on the secretory conception of the hepatic glycogen. As will be shown in this chapter, the conclusion arrived at on the basis of the secretory conception enables one to correlate all the known facts and, in particular, to understand the action and interaction of the endocrine organs on carbohydrate metabolism. The storage conception, on the other hand, leads to conclusions which cannot be reconciled with each other or with observed facts.

An example will make this point clear. In a normal individual the blood sugar reaches a minimal level during fasting which is fairly constant. If carbohydrate is ingested the blood sugar rises during the first hour and then falls to reach again the minimal level. In various pathological conditions, notably diabetes mellitus, this normal blood-sugar curve shows alterations : the rise of the blood sugar after the ingestion of glucose is prolonged, and in diabetes mellitus there is in addition a higher minimal level of the blood sugar in the fasting condition. On the storage conception of the glycogenic function the interpretation of the normal blood-sugar curve is that the liver withdraws glucose from the blood and thus ensures the rapid return of the blood sugar to the constant minimal level, so that the glycogenic function of the liver is conceived as the main factor in preventing a prolonged rise of the blood sugar. It follows from this conception

that a prolonged rise of the blood sugar should be interpreted as hepatic insufficiency and it is so interpreted by MacLean, for instance. The same interpretation of hepatic insufficiency is given to the higher level of the blood sugar in diabetes. But if a hepatic insufficiency is produced experimentally by removal of the liver or by severe liver lesions one does not get hyperglycæmia, but a rapid hypoglycæmia (Mann and Magath). If now glucose is injected into a hepatectomised animal the blood sugar rises. But it rapidly falls again, and even if large doses of glucose (5 gm. per kilo body weight) are given hypoglycæmia appears again after an hour. This is obviously contrary to the storage conception, which teaches that the return of the blood-sugar curve to the normal level after the initial rise following the introduction of glucose is brought about mainly by the liver withdrawing glucose from the blood and storing it. If that explanation were correct the injection of glucose into a hepatectomised animal should produce a greatly prolonged rise in the blood sugar.

The rapid fall of blood sugar in hepatectomised animals to values below the minimal fasting level also shows clearly that the peripheral cells continue to burn glucose at a rapid rate, even when the percentage of glucose in the blood is low.

Another example of the inadequacy of the storage conception is the effect of thyroid feeding. It was the study of the condition of carbohydrate metabolism in thyroid feeding which led us first to question the validity of the orthodox storage conception and to develop a different conception which we afterwards found to be identical with the original secretory conception of Claude Bernard. As the evidence obtained from the experimental findings in experimental hyperthyroidism, which have since been confirmed by Kuriyama and by Sanger, is particularly clear, we shall discuss it in some detail.

The facts are as follows : Thyroid feeding in rats and in

cats kept on a carbohydrate rich diet produces a rapid disappearance of glycogen from the liver, so that after three to five days the liver contains only a trace of glycogen. The glycogen of the muscles remains unaffected, and no evidence of a hypothetical store of an unknown carbohydrate has been obtained. The values of the blood sugar remain within their normal limits and there is no glycosuria. There is loss of weight. The gaseous metabolism shows a great increase and so does the protein metabolism, as evidenced by an increased nitrogen excretion in the urine. If the respiratory quotient is determined in hourly intervals for the first eight hours after a carbohydrate rich meal the values found in the first two or three days of thyroid feeding are slightly higher than the normal values, but distinctly lower during the later stages (third to fifth day) of thyroid feeding, when the glycogen has disappeared from the liver. The remarkable result has been obtained that in the later stages of thyroid feeding the respiratory quotient may be as low as ·85 or ·80, even immediately after a meal so rich in carbohydrates that in the normal animal the respiratory quotient at the same hour reaches the value of 1. When the increased nitrogen excretion in the urine is analysed, so as to give a picture of the nitrogen distribution in the urine, the result obtained is the same as that observed when carbohydrates are withdrawn from the diet or in clinical or experimental diabetes mellitus. It is interesting to compare the two conditions by reference to the following table :

	Experimental Hyperthyroidism.	Diabetes Mellitus.
Protein metabolism	Increased	Increased
Liver glycogen	Absent	Absent
Respiratory quotient	Low	Low
Weight and fat	Loss	Loss
Gas. metabolism	Increased	Not increased
Blood sugar (fasting)	Normal	Increased
Glycosuria	Absent	Present

It will be seen that the two conditions have the first four features of this table in common, but differ in the last three. We shall see presently that both the similarities and the dissimilarities are not merely accidental ones obtaining between two unrelated conditions, but find an explanation in the secretory conception of the glycogenic function.

Whatever view of the glycogenic function one adopts, the observed facts which require explanation are as follows: In experimental hyperthyroidism on a carbohydrate rich diet no carbohydrate is present in the liver, the muscles do not contain more glycogen; no other store of carbohydrate can be found, no carbohydrate is deposited as fat, no sugar passes out in the urine, but there is an increase in the basal metabolism. The fate of the carbohydrate supplied in the food can therefore only be accounted for by the rise in the basal metabolism. That means that in spite of the lowered respiratory quotient in experimental hyperthyroidism more carbohydrate is oxidised than in animal organism, and that is the fundamental difference between this condition and diabetes mellitus.

How can the condition of metabolism in experimental hyperthyroidism be explained on the storage conception of the glycogenic function? On that conception we should have to assume that the thyroid hormone inhibits the storage of glycogen in the liver. That, in fact, was the conclusion we drew at first from our results. If that were so the blood sugar on a diet rich in carbohydrates should give very high values, and it should be possible to induce alimentary glycosuria with comparative ease. As already stated no glycosuria was observed in rats and cats. Unpublished experiments on dogs, carried out specially to test this point, in which large quantities of sugar were given by the mouth failed to show a diminished sugar tolerance in thyroid-fed animals.

If we pass over these difficulties and deal with the

increased oxidation of sugar we would expect to find a reduction of the protein metabolism, as one finds in a normal animal when more carbohydrate is oxidised. But the reverse is the case: the protein metabolism is increased and behaves as if no carbohydrates at all were present in the diet. Moreover, the respiratory quotient is lower than normal instead of being higher. Another difficulty appears, when we try to explain the increased oxidation of carbohydrates in experimental hyperthyroidism by postulating for the thyroid hormone a direct stimulating action on the oxidative processes of the peripheral cells. Such an explanation is ruled out by the following considerations. There is no direct evidence that thyroid has such an effect. Further, if it existed we could explain on the storage conception that the glycogen disappears from the liver, but if the thyroid feeding continued after the glycogen had disappeared it should lead to a hypoglycæmia. But this does not occur. Again, if the thyroid hormone stimulated the peripheral cells directly to increased oxidation of carbohydrates the removal of the thyroid gland should tend to favour the production of a glycosuria or, at least, a diminished tolerance for sugar, while its administration in diabetes mellitus should improve the glycosuria. The experimental test shows that the sugar tolerance is not diminished in a normal animal by removal of the thyroid gland, nor is it diminished in myxœdema; in diabetes mellitus removal of the thyroid diminishes the glycosuria while thyroid feeding increases the glycosuria.

What has been said is sufficient to show that the storage conception of the glycogenic function involves us in a maze of contradictions and cannot explain the carbohydrate metabolism in experimental hyperthyroidism. Some authors who have dealt with the subject ignore these difficulties, others acknowledge them by stating that the relation of the thyroid gland to carbohydrate metabolism is "obscure". But the obscurity

vanishes when we replace the storage conception by the secretory conception of the glycogenic function. On the secretory conception, as will be seen, the action of the thyroid hormone appears as a stimulus to the glycogenic function (instead of the inhibition postulated by the storage conception) and then all the difficulties and contradictions are resolved.

On the secretory conception of the glycogenic function the liver forms carbohydrate autonomously and irrespective of any supply of carbohydrate in the food. If no carbohydrate is given in the diet the liver uses protein and probably also fat for the formation of glycogen. On this view the liver forms glycogen as its specific secretion, in the same way as any other gland, and secretes it into the blood-stream as glucose automatically when the blood sugar has reached its minimal level. The glycogenic function of the liver maintains in this way the constant level of the blood sugar in the fasting condition or when no preformed carbohydrate is supplied with the food. Like any other secreting gland the secretion of the liver glycogen is under nervous control, namely the splanchnics, so that glucose is also secreted into the blood in response to the stimulation of these nerves, whether directly or through hormones, such as adrenalin. On the secretory conception the glycogenic function is therefore concerned with preventing the blood sugar from *falling below* the minimal level, and not, as in the storage conception, with preventing the blood sugar from *rising above* the minimal level. This is confirmed by the fact, already referred to, that removal of the liver or severe liver lesions produce a hypoglycæmia. Again, on the secretory conception any deviation of the blood sugar involving a rise in the blood sugar can only be due to hepatic hyperactivity, and not to hepatic insufficiency as the storage conception demands.

If we regard the metabolism in experimental hyperthyroidism in the light of the secretory conception as the result of a stimulus of the glycogenic function, as has

been done in the preceding chapter, all the observed and apparently contradictory phenomena fall naturally into their proper place. As the result of hepatic hyperactivity the liver secretes more glucose into the blood and forms more carbohydrate from protein and fat. Hence the increased nitrogen excretion and loss of fat, the low respiratory quotient with an increased oxidation of carbohydrates. The increased metabolism is due partly to the greater influx of glucose (" metabolism of plethora ") and partly to the increased cellular activity resulting from stimulation of the sympathetic. The blood sugar is therefore burned away as quickly as it is secreted into the blood, and remains within normal limits.

The same difficulty is experienced when we try to explain the action of insulin on the basis of the storage conception. The vast literature which has accumulated in a few years around that problem without furnishing a consistent explanation is eloquent evidence of the inadequacy of the storage conception. We shall see that on the secretory conception the action of insulin finds an explanation as an inhibition of the glycogenic function.

These examples will be sufficient to show that it is of fundamental importance to know whether the liver glycogen is to be regarded as a store of carbohydrate, or as a specific secretion of the liver cell—its " internal secretion ". What then is the evidence for or against these two conceptions ? It is, fortunately, easy to answer this question. The only direct argument in support of the storage conception is the fact that on a carbohydrate rich diet the liver glycogen increases. It is obvious, however, that this can be explained just as readily on the ground that on such a diet the blood sugar is kept on a higher level, so that the liver is never called upon to secrete glucose. As it continues to form glycogen without secreting any glucose the glycogen is bound to accumulate in the liver.

Against the storage conception there is conclusive evidence. It was formulated when it was believed that the blood sugar always remained constant and was not affected by the intake of carbohydrate in the food. It was held then that the liver prevented the ingested carbohydrate from reaching the systemic circulation, by holding it back, transforming it into glycogen and depositing it within the cells. The anatomical position of the liver which compels all the blood from the intestine to pass through it before it could reach the systemic circulation was regarded as lending support to such a view. When the refinement of biochemical methods showed that the blood sugar showed wide fluctuations with every meal containing carbohydrates, the whole conception was deprived of its basis and ought to have been abandoned, because there has always been strong evidence against the storage conception. But when an error has once found its way into physiological text-books it soon reaches by repeated reiteration the dignity of a dogma, and the evidence against it is ignored. The chief evidence against it can be summarised briefly by stating that it has been shown in the most convincing manner and in many different ways, that the liver forms glycogen whether carbohydrate is supplied in the food or not. Indeed, it forms glycogen even when no food is supplied at all. This evidence is not new. Some of it is as old as the discovery of glycogen. For as soon as Claude Bernard discovered glycogen he at once recognised the importance of determining whether it was merely a store of carbohydrate. By simple but conclusive experiments he showed that the formation of glycogen by the liver is as independent of any supply of carbohydrate material in the food or of any supply of food as is the formation of its specific secretion by any other gland. He therefore invented the term " internal secretion " to designate the hepatic glycogen, and he never ceased to emphasise the secretory aspect of the glycogenic function.

Our present knowledge of carbohydrate metabolism has greatly advanced since Claude Bernard, but all the facts that have since come to light, such as the effects of thyroid feeding, the action of insulin, the effect of hepatectomy, confirm his conception.

They remain inexplicable on the storage conception. It would be merely wearying the reader to illustrate this statement point by point. We have given several examples of it in a separate paper. The opposite viewpoint can readily be obtained by reading the recent book of MacLeod on *Carbohydrate Metabolism and Insulin*, or the recent lecture of H. Maclean on " Carbohydrate Metabolism in Health and Disease ", both of whom base their conclusion on the storage conception, although Macleod does admit that there is perhaps something to be said for the secretory conception.

We propose, therefore, to develop this latter conception and its implication and to refer merely in passing to the fallacies of the storage conception.

It has long been known that the liver can form glycogen in the absence of any carbohydrate in the food and even of any food at all. The liver may be made almost free from glycogen by inducing by means of strychnine violent muscular contractions in a fasting animal. If the effect of strychnine is allowed to pass off and the fasting is continued, glycogen will again make its appearance in the liver. Another striking example is reported by Pflüger, who found 24·3 gm. glycogen (= 4·8 per cent) in the liver of a dog which had been kept without food for twenty-eight days. The glycogen content of the liver of a number of normal well-fed dogs is given by Pflüger as varying between 4·3 and 18·7 per cent. The effect of starvation was much more pronounced in the glycogen content of the muscular tissue, which amounted only to 0·16 per cent in starved animals as against 0·7 to 3·7 per cent of glycogen found in the muscles of well-fed dogs. Claude Bernard showed that the liver-cells have the power to form carbohydrate

material from protein, and do so when no supply of preformed carbohydrate is available in the food. A consideration of these facts leads to the conclusion that glycogen represents the specific product of the autonomous secretory activity of the liver-cell, in the same way as trypsinogen, for instance, is the product of the pancreatic cells and adrenalin that of the medullary cells of the adrenal. If we wish to understand the function of an organ we study the effects resulting from its removal. As already stated hepatectomy or even lesions of the liver produce a fall in the blood sugar so severe that the animal can be kept alive only by the repeated injection of glucose. That shows that a certain minimal level of the blood sugar is essential for life and that it is the function of the liver to maintain this minimal level by secreting glucose into the blood. In a number of conditions glycogen disappears from the liver: exposure to cold, injection of adrenalin, injections of β-tetrahydronaphthylamine, thyroid feeding, removal of the pancreas. Now in these various conditions the blood sugar does not fall below the minimal level when the glycogen has disappeared from the liver. On the contrary in all of them the blood sugar is either above the minimal level or shows a prolonged hyperglycæmia after the injection of glucose. It is clear, therefore, that the liver continues to secrete large amounts of glucose, even when there is only a trace of glycogen present in the liver cells. There is nothing paradoxical or contradictory in this statement. In other internally secreting glands the specific secretion diminishes and may even disappear when the gland is stimulated to activity, but the gland continues to function and to pour out its secretion because it is also stimulated to a new formation of the specific secretion. Thus, if the thyroid gland is stimulated by exposure to cold or by the injection of β-tetrahydronaphthylamine, the colloid disappears from the alveoli, but the gland continues to act. In Graves' disease where the

thyroid is hyperactive the thyroid alveoli contain little or no colloid. It is only in the inactive thyroid gland—after exposure to heat, for instance—that the specific secretion accumulates and the alveoli are distended with colloid. The amount of glycogen present at a given moment in the liver, like the amount of colloid in the thyroid or the amount of adrenalin in the adrenal medulla, represents the balance between the rate at which it is formed and that at which it is secreted. If the glycogenic function is at the height of its activity and glycogen is being secreted as rapidly as it is being formed, the amount of glycogen present in the liver may be very small. That accounts for the absence of glycogen in experimental hyperthyroidism and in a number of other conditions to be discussed presently. Markovicz, working in Macleod's laboratory, has recently carried out a number of experiments which confirm this view.

It follows, therefore, that the presence or absence of glycogen is not a measure of the activity of the glycogenic function. It is important to emphasise this statement because it is on this point that the secretory conception differs so fundamentally from the storage conception. An increase of glycogen in the liver means hyperactivity on the storage conception, it means inactivity on the basis of the secretory conception. The absence of glycogen is interpreted on the storage conception as exhaustion of the "carbohydrate reserves", and therefore insufficiency of the glycogenic function. But on the secretory conception, absence of glycogen is most frequently associated with conditions which represent increased activity of the glycogenic function. It cannot be too strongly emphasised that the notion of an "exhaustion of carbohydrate reserves" which plays at present so large a part in the explanation of the various phenomena of carbohydrate metabolism is a fictitious one and ought to disappear from the literature altogether.

In order to make this important point quite clear a

crude analogy with the water supply of a house may serve. The cistern represents the liver, the water in it the glycogen, the water flowing out of the cistern the blood sugar. The storage conception is represented by a cistern which is only periodically filled—say by rain. The water in that cistern represents a store. It diminishes by exactly the same amount that is allowed to flow out of the cistern when the water taps in the house are opened. When the cistern is empty the store is exhausted and the taps run dry. In such a system the *amount of water in the cistern* is the determining factor. The secretory conception is represented by a cistern connected with a water supply, such as exists in a town house. Here by the device of the ball valve water is allowed to flow into the cistern whenever water flows out of it. The amount of water is therefore not a " store ", but represents the balance between inflow and outflow. As long as this system is in working order the taps will never run dry, even though the amount of water in the cistern may be very low. The taps will run dry only if either the outflow or the inflow of the cistern, or both, are blocked. With such a system the determining factor is not the amount of water in the cistern, but the *amount of water flowing through the cistern*. Obviously with such a system the amount of water flowing through it may be very large, although the amount of water actually present in the cistern at a given moment may be small. Conversely, the amount of water in the cistern may be large, while little or no water is flowing through it. If we wish to know the rate at which this system is working we must determine the inflow and the outflow from the cistern. Expressed in terms of carbohydrate metabolism the outflow is represented by the behaviour of the blood sugar; the inflow, as we shall see presently, by changes in protein metabolism as shown by the nitrogen excretion in the urine.

The presence or absence of glycogen in the liver by itself does not have, therefore, the importance which is at

present attributed to it, and does not give us a reliable criterion of the activity of the glycogenic function. It has to be interpreted in the light of other considerations, which enable us to determine whether the liver is secreting glucose or not. Thus in a fasting animal a rise in the blood sugar above the minimal level indicates increased activity, a fall below the minimal level means diminished activity.

But it would be a fallacy to invert this statement and to conclude that the absence of changes in the blood sugar of the fasting animal proves the absence of changes in the glycogenic function. Like the liver glycogen the blood sugar must be interpreted as representing the balance between inflow from the liver and consumption by the muscles. If, as the result of a slow persistent stimulation, such as occurs, for instance, in experimental hyperthyroidism, the consumption of glucose increases *pari passu* with an increased inflow from the liver, the blood sugar of the fasting animal will show no marked deviation from the normal, although the glycogenic function is for reasons given above in a state of increased activity.

Even then a difference can be demonstrated by following the blood-sugar curve after the injection of glucose : the rise is then greater and more prolonged in the thyroid-fed animal than in the normal animal (Marks, 1926). It may be noted in passing that the paradoxical results which Burn and Marks obtained after very prolonged feeding with thyroid gland (twenty days) in rabbits are due to secondary changes induced by prolonged feeding in the adrenal gland, which are described in the following chapter, and in the pancreas (unpublished results), and not, as these authors claim, to an exhaustion of the "glycogen reserve"; for these results are not obtained in such an animal as the rat, in which thyroid feeding induces the disappearance of glycogen from the liver in a very much shorter time (three to five days) than in the rabbit.

If we apply these considerations, we can group the following conditions according to their effect on the glycogenic function :

GLYCOGENIC FUNCTION.

Increased.	Diminished.
Thyroid hormone Cold Adrenalin Sympathetic fever	Liver lesions Hepatectomy Insulin

This table shows that within the organism the glycogenic function is being played upon by two antagonistic influences, the one stimulating it, the other inhibiting it. Stimulation occurs when the thyroid and adrenal glands are aroused to active secretion, inhibition is the result of the increased internal secretion of the pancreas.

Thus the injection of adrenalin increases the blood sugar. Owing to the general sympathetic stimulation there is an increased activity of the cells, for instance a more rapid heart beat, and the secreted sugar is oxidised. Insulin, on the other hand, inhibits the secretion of glucose by the liver, and, at the same time, insulin has a peripheral effect on the cells, especially the muscle cells : it increases the absorption of glucose by the cells. It is thus possible to explain the hypoglycæmia of insulin as the result of the combination of these two actions : inhibition of the glycogenic function and increased absorption by the muscle cells. All attempts to explain the hypoglycæmia of insulin on the basis of the storage conception have, so far, failed and are bound to fail.

Our conception that insulin, apart from its peripheral effect, has also a central effect on the liver, inhibiting the formation of carbohydrate from protein and possibly fat, has also been developed by Lesser and by Laufberger, and has now also been accepted in the most recent work of Dale and his collaborators.

If we now go a step further and consider the effects of removing either the inhibitory or the stimulating influence operating within the organism, we get the following results. If by pancreatectomy the inhibiting influence is removed the stimulating influence of the thyroid and adrenal glands preponderates. Pancreatectomy is therefore tantamount to a stimulation of the glycogenic function. The condition may be likened to the acceleration of the heart when the inhibiting influence of the vagus is removed. The glycogen-free liver of the diabetic organism corresponds therefore to the glycogen-free liver of the organism in hyperthyroidism. The increased nitrogen excretion in diabetes mellitus corresponds to the increased nitrogen excretion in hyperthyroidism with its similar nitrogen distribution in the urine. In both conditions it is a manifestation of the hyperactivity of the glycogenic function. The hyperactivity of the glycogenic function of the liver in diabetes mellitus was quite clearly recognised by Claude Bernard. In fact, he explains diabetes mellitus as the result of an increased sugar production by the liver. He writes (*Leçons sur le diabète*, p. 437): "Le sucre est versé dans le sang en quantité anormale, d'où hyperglycémie et glycosurie, mais la source hépatique n'est pas épuisée pour cela, elle continue à assimiler les matériaux propres à former le glycogène et par suite le sucre ; elle redouble, pour ainsi dire, d'activité pour remplacer le sucre éliminé, elle épuise l'organisme pour suffire à cette production, à cette dépense désordonnée en matières sucrés." We know now that the hyperactivity of the glycogenic function and the resultant hyperglycæmia is not sufficient to produce glycosuria, unless there is also an impaired oxidation of glucose by the cells. But this latter factor has been considered too exclusively in recent work on diabetes mellitus and the hepatic factor has been unduly neglected. Insulin corrects both factors ; it inhibits the hyperactivity of the glycogenic function and it facilitates the oxidation of carbohydrates by the cells.

Experimental evidence is available which demonstrates the importance of the hepatic factor in diabetes mellitus. Recently Hendrix and Sweet have shown that the sugar excretion of a depancreatised dog is diminished when the liver is excluded from the circulation by an Eck's fistula.

Since the hyperactive liver after pancreatectomy is steadily secreting glucose into the blood the blood sugar rises. But since in the absence of the pancreatic hormone (insulin) the muscle cells do not absorb glucose as effectively as in a normal animal, the cells do not react to this inflow of sugar into the blood by an increased oxidation as they do after adrenalin or thyroid feeding, and so the blood sugar rises to such a high level that glycosuria occurs and the condition of diabetes mellitus is established.

The converse condition to pancreatectomy is established by thyroidectomy or by adrenalectomy, when a stimulating influence is removed. These two conditions are therefore tantamount to an inhibition of the glycogenic function. The inhibition is only partial, because if the adrenals are removed the stimulating effect of the thyroid remains and *vice versa*. In Addison's disease we find accordingly the blood sugar to be frequently, though not always, below the normal (Rosenow and Jaguttis, 1922). Similarly, conditions, such as exposure to a warm environment, which diminish the activity of the thyroid and adrenal gland inhibit the glycogenic function. The following additions can therefore be made to the table given above :

GLYCOGENIC FUNCTION.

Increased.	Diminished.
Pancreatectomy	Thyroidectomy Adrenalectomy Heat

These conclusions may be summarised in the following diagram :

It shows in a concise form how the various conditions which are known to affect carbohydrate metabolism,

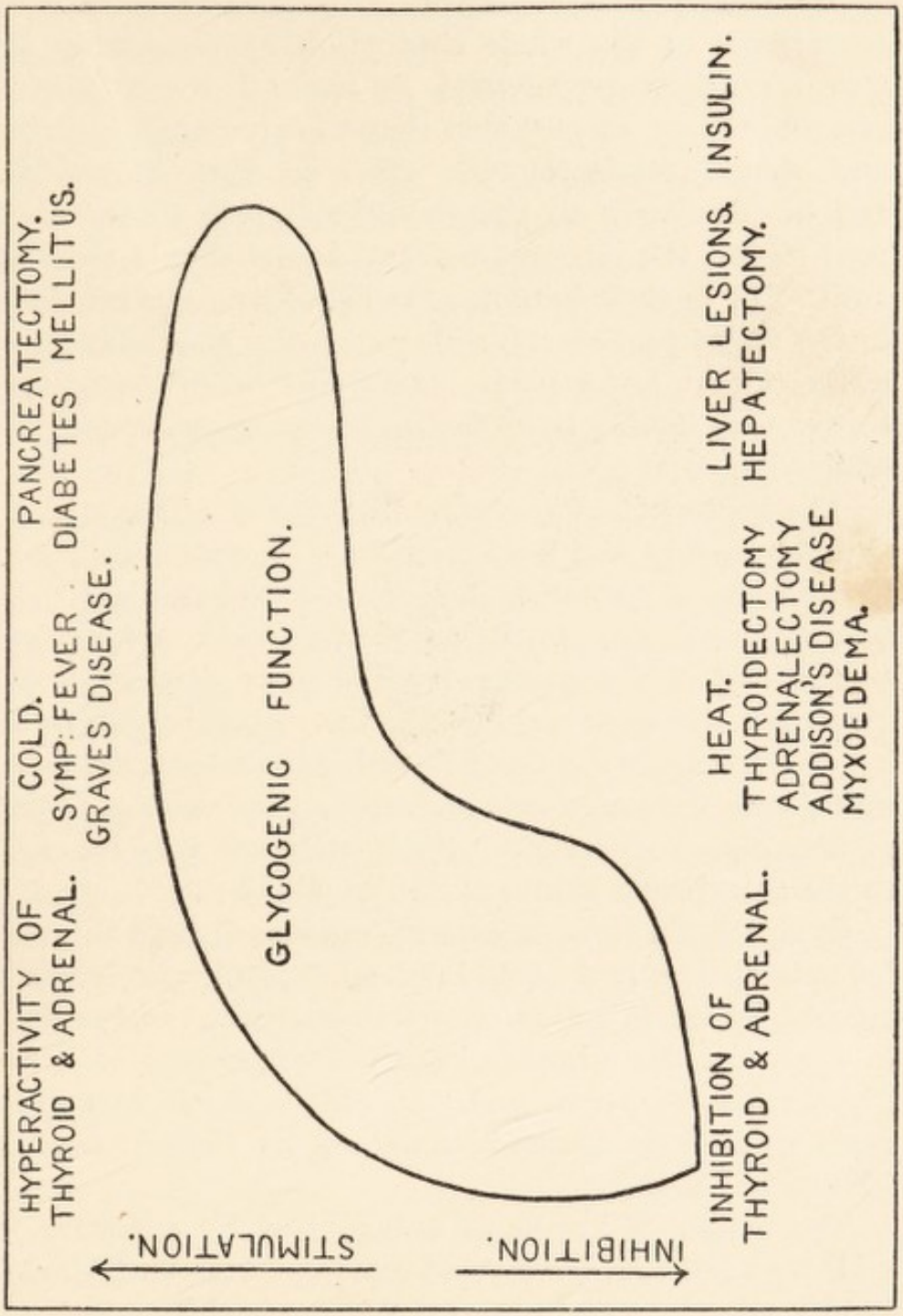

FIG. 10.

and the interrelationship of which has hitherto been inexplicable, fall into an orderly arrangement if they are grouped according to their actions on the

glycogenic functions of the liver as interpreted in these pages.

By means of this diagram it is possible to test the correctness of the whole conception by combining any two conditions represented in it. All the conditions given in the upper part stimulate the glycogenic function, and should reinforce each other in their stimulating action. Similarly all the conditions given in the lower part inhibit the glycogenic function and should reinforce each other in their inhibitory action. Any one condition in the upper part should antagonise any condition represented in the lower part. The following examples may be given as having been demonstrated experimentally or clinically :

The glycæmia of pancreas diabetes is aggravated by thyroid feeding and by adrenalin. It is diminished by thyroidectomy (Lorand, McCallum, Rohdenburg, Friedman and Gottesman). Removal of the adrenals previous to removal of the pancreas prevents or diminishes the glycosuria (Houssay and Lewis). In cases of diabetes, cold, hyperthyroidism, the fever resulting from bacterial infections, and toxæmias are known to increase the hyperglycæmia and glycosuria. Such cases are very resistant to the therapeutic action of insulin (Wilder).

Sympathetic fever is induced more easily in a thyroid-fed animal than in a normal animal. The hyperglycæmia induced by the injection of certain bacterial vaccines fails to appear if the adrenals have been removed, or if the thyroid has been removed. It can be made to appear again in a thyroidectomised animal by thyroid feeding (Evans and Zeckwer).

The action of insulin is antagonised by exposure to cold, by adrenalin, by thyroid feeding (Burn and Marks) and by some bacterial toxins (Lawrence and Buckley) ; it is favoured by exposure to heat and by thyroidectomy. Patients suffering from Graves' disease are less sensitive to insulin (Lawrence Wilder).

Removal of the adrenals produces an inhibition of the glycogenic function which manifests itself in the same way as the inhibition produced by insulin, namely, by a lowering of the blood sugar below the normal value in fasting animals. In mice this inhibition may go so far as to induce hypoglycæmic convulsions (Cori and Cori). One might predict from this table that severe liver lesions and Addison's disease would make the organism more sensitive to the action of insulin. Conversely infections, especially those associated with a high fever, would have the opposite effect. As already stated, in cases of diabetes bacterial infections and toxæmias are known to render such cases more resistant to insulin.

It may be necessary to point out that in this diagram the antagonism between the different conditions refers only to the glycogenic function and not necessarily to the various conditions as a whole. Insulin counteracts pancreatectomy. But insulin is not a complete antagonist to sympathetic stimulation as a whole, and therefore insulin can antagonise only those effects of sympathetic stimulation which are due to increased glycogenic function. These considerations are perhaps more obvious in dealing with the effects of heat and cold in sympathetic fever, as produced by the injection of β-tetrahydronaphthylamine. The general sympathetic stimulation of that condition involves increased heat production and diminished heat loss. Cold by stimulating the glycogenic function might be thought to enhance the effect of the drug, but in so far as cold increases heat loss it antagonises the rise in temperature, while heat by further diminishing the heat loss intensifies the effect. Since we measure the effect of the drug by the rise in temperature and since death in this condition is due to hyperpyrexia, the effect of exposure to heat is to aggravate the condition, and of exposure to cold to antagonise it.

On the basis of this conception one can predict that insulin should be of benefit in Graves' disease though it

could not cure it. This has been shown to be the case by Lawrence. Insulin cannot cure this disease since it does not act directly on the thyroid, the hyperactivity of which is the source of the trouble. Insulin antagonises only the stimulating effect on the glycogenic function and thereby may reduce metabolism. But in doing this it counteracts only one symptom of the disease.

So far we have only dealt with that aspect of the glycogenic function which corresponds to the outflow from the cistern, namely the secretion of glucose into the blood-stream. But there is also to be considered the inflow : the formation of glycogen. It has been customary —no doubt owing to the perverted conception of glycogen as a " store " or " reserve " of carbohydrate—to treat the formation of glycogen, or glycogenesis, and the passage of glucose into the blood, or glycogenolysis, as if they were two entirely separate processes occurring in the liver cells which proceed in two separate test tubes, so to speak, and which can be stimulated separately and inhibited separately. But if we regard the glycogenic function as representing the secretory activity of the liver cells, we come to see that secretion and formation of glycogen are closely linked up. In every secreting cell the stimulus to secretion is at once a stimulus to the new formation of the specific secretion. Increased glycogenic function involves necessarily the increased formation of glycogen by the liver. In what way does this increased formation of glycogen by the liver manifest itself ?

It is known that the liver forms glycogen from carbohydrate when an abundant supply is given and from proteins if no supply of carbohydrate in the food is available. When, after supplying to an animal a constant diet of protein and carbohydrates, the carbohydrate is replaced by a caloric equivalent of fat, the nitrogen excretion rises. This phenomenon is known as " the protein-sparing action of carbohydrates ". It has never been explained, and cannot readily be explained on the storage conception.

The secretory conception affords the interpretation, that in the absence of carbohydrates from the food the liver is compelled to use protein for the formation of glycogen. Now exactly the same phenomenon appears if the animal continues on the same diet of protein + carbohydrates, but receives thyroid gland. There is the same increase in the nitrogen excretion which occurs when carbohydrate is replaced by fat in the diet, and even the distribution of the nitrogen in the urine is the same, although the animal receives abundant carbohydrate and oxidises it. This effect of thyroid feeding is quite inexplicable on the storage conception. The secretory conception has taught us that when in hyperthyroidism the glycogenic function is stimulated to increased activity, and more glucose is secreted into the blood, more glycogen is also being formed by the liver cells. To accomplish this the liver cells have to attack more protein. We may say, therefore, that increased glycogenic function, in so far as it increases the *formation* of glycogen, manifests itself by a rise in the nitrogen excretion.

This conclusion is confirmed by applying it to the conditions given above as stimulating the glycogenic function. For an increased nitrogen excretion has been observed not only after thyroid feeding, but also after adrenalin and β-tetrahydronaphthylamine. It is also a characteristic result of pancreatectomy. The increased protein breakdown in Graves' disease, diabetes mellitus and in fever are also manifestations of the increased activity of the glycogenic function. The effect of cold on nitrogen metabolism does not appear ever to have been studied experimentally, but the tendency to obesity in persons living in a warm environment is well known. One characteristic feature of the increased nitrogen excretion is its delayed onset. After adrenalin and β-tetrahydronaphthylamine, for instance, it begins on the day following the administration. The process involves deamidisation, conversion of the detached ammonia into urea and its

excretion, so that obviously the nitrogen excretion must lag behind the immediate effect on the blood sugar.

The increased nitrogen excretion resulting from stimulation of the glycogenic function is of special interest in relation to the explanation of fever, because one of the characteristic effects on metabolism is an increased protein destruction. This is usually attributed to the bacterial toxins breaking down tissue protein. On the secretory conception it is the result of the stimulation of the glycogenic function.

After giving insulin in moderate doses to normal well-fed animals a diminished nitrogen excretion has been observed, as is to be expected if insulin inhibits the glycogenic function. Similarly it has been found that carbohydrate and insulin given together " spare " more protein than the same amount of carbohydrate given without insulin (Janney and Shapiro). The effect of insulin on protein metabolism manifests itself more clearly when insulin is given to pancreatectomised animals. Then the nitrogen excretion falls indicating that the hyperactive glycogenic function of the diabetic animal, as the result of which glucose is poured into the blood and protein is destroyed, is being inhibited.

Summary.

If the argument in the preceding pages has been long and perhaps involved, this is due to the necessity of contrasting the two opposed conceptions of the glycogenic functions. The secretory conception itself is simple. The whole argument may be summarised by saying that in the light of the secretory conception the liver becomes the central organ of metabolism as the heart is the central organ of the circulation. Its function is to supply the peripheral cells with the chemical fuel—glucose—which they need for their activity, by constantly forming carbohydrate in the form of glycogen, if necessary from proteins and possibly also from fats, and by passing it out

into the blood as glucose, so as to maintain in the blood a minimal level of glucose concentration below which the peripheral cells cannot function properly. The interrelationship of carbohydrate metabolism with protein and fat metabolism is therefore centred in the glycogenic function. If this function is stimulated to increased activity there is, on the one hand, an increased secretion of glucose into the blood, which produces a hyperglycæmia, except in those conditions in which the oxidation of glucose by the tissues is increased *pari passu* with the increased secretion of glucose, as, for instance, in hyperthyroidism. On the other hand, there is an increased formation of glycogen which manifests itself by an increased protein destruction and disappearance of fat. If it is inhibited there is a diminished passage of glucose into the blood, resulting in a hypoglycæmia and a diminished formation of glycogen, which manifests itself by a diminished protein metabolism and nitrogen retention. It is possible that constitutional obesity may find an explanation in an inhibition of the glycogenic function. The behaviour of the blood sugar in the fasting condition represents, therefore, the much-desired test for hepatic efficiency so far, at any rate, as the glycogenic function is concerned : a hyperglycæmia means increased activity, a hypoglycæmia an inhibition of hepatic activity. Similarly the varying resistance to the action of insulin can be interpreted as variations in the degree of hepatic activity. The thyroid and adrenal hormones stimulate the glycogenic function, the pancreatic hormone inhibits it. Sympathetic stimulation, which arouses the peripheral cells to increased activity, also stimulates the liver to form more glycogen and to pour more glucose into the blood. Considered teleologically this effect presents a most efficient mechanism to correlate an increased activity of the peripheral cells and an adequate supply of fuel. The efficiency of this correlation is obviously of vital importance to the maintenance of the organism and,

although of special interest from the point of view of heat regulation, it has not hitherto received an adequate explanation.

The problem of the interrelationship of the thyroid, adrenal and pancreas on metabolism finds its solution in the action of their hormones on the glycogenic function. There is an antagonism between the stimulating action of the thyroid and adrenal hormones and the inhibition by the pancreatic hormone. But this antagonism is restricted to the action on the glycogenic functions and does not extend to the action of these hormones on the carbohydrate metabolism of the peripheral cells—heart, muscle, etc.

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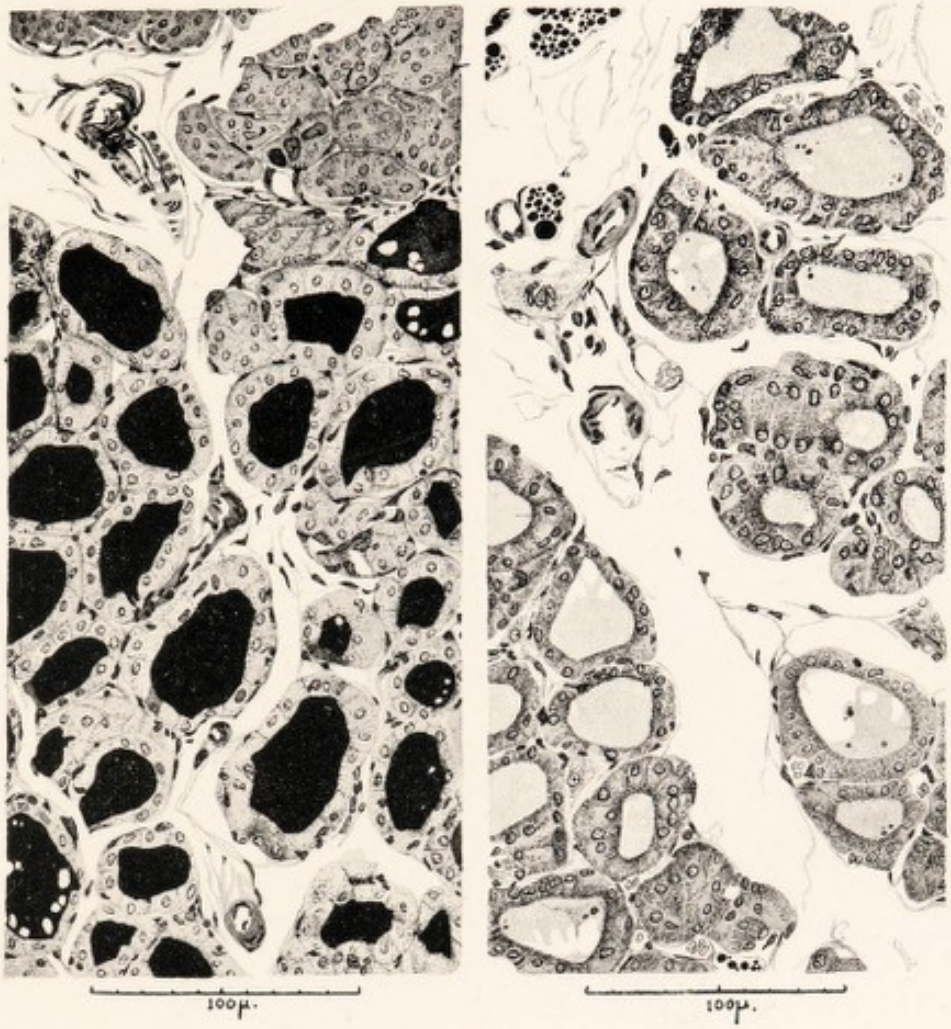

PLATE 16.

Thyroid gland of two young rats kept on ordinary diet. The left-hand figure represents the thyroid with part of the parathyroid of a rat fed on dried thyroid gland (0·3 gm. per day) for three days. The right-hand figure is from a normal control rat. The sections were stained on the same slide with Heidenhain's iron-alum hæmatoxylin method. The alveoli in both glands are uniformly filled with colloid which retains the hæmatoxylin more firmly in the thyroid-fed rat. This is attributed to the lessened demand for the thyroid hormone in the thyroid-fed rat. Schridde $\times \frac{250}{1}$.

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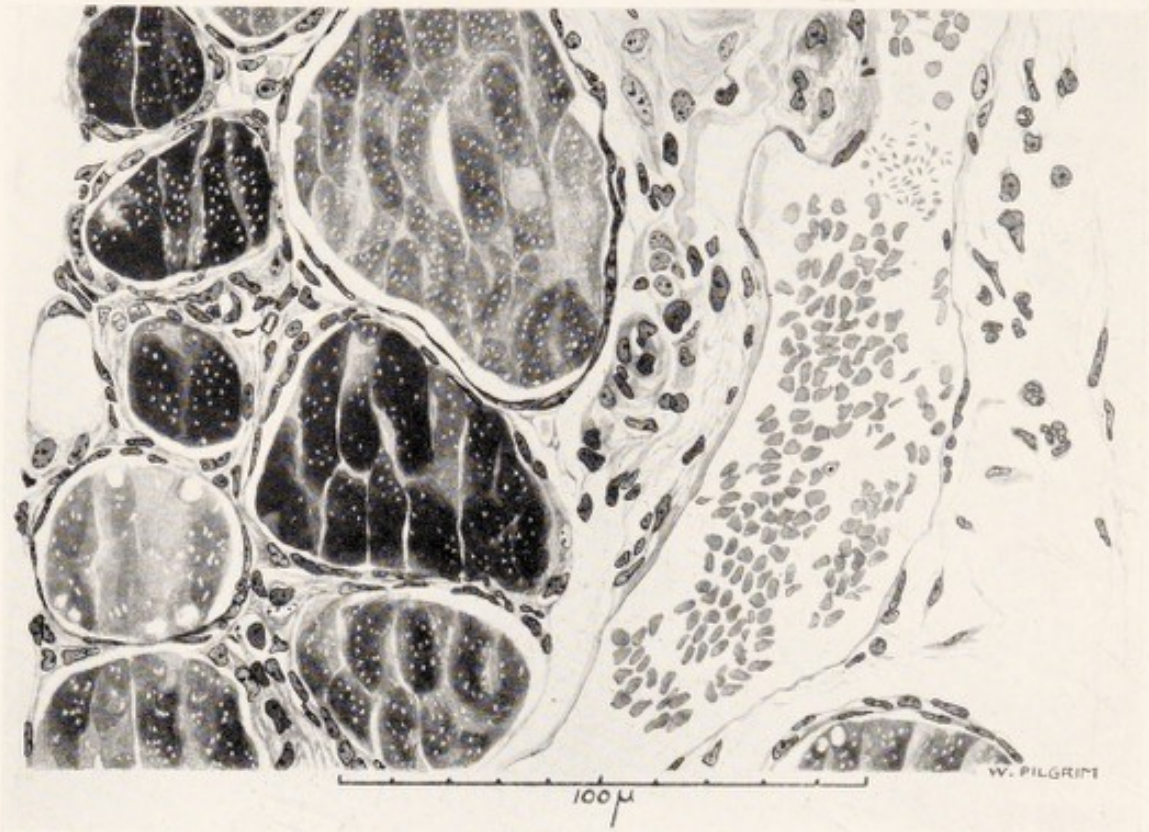

PLATE 17.

Thyroid gland of mouse kept on small doses of dried thyroid gland for three and a half months. The alveoli are widely distended with deeply staining colloid which contains some crystalline material. The epithelium lining the alveoli is atrophied. Schridde $\times \frac{500}{1}$. Compare with Text Figures 3, 4 and 5.

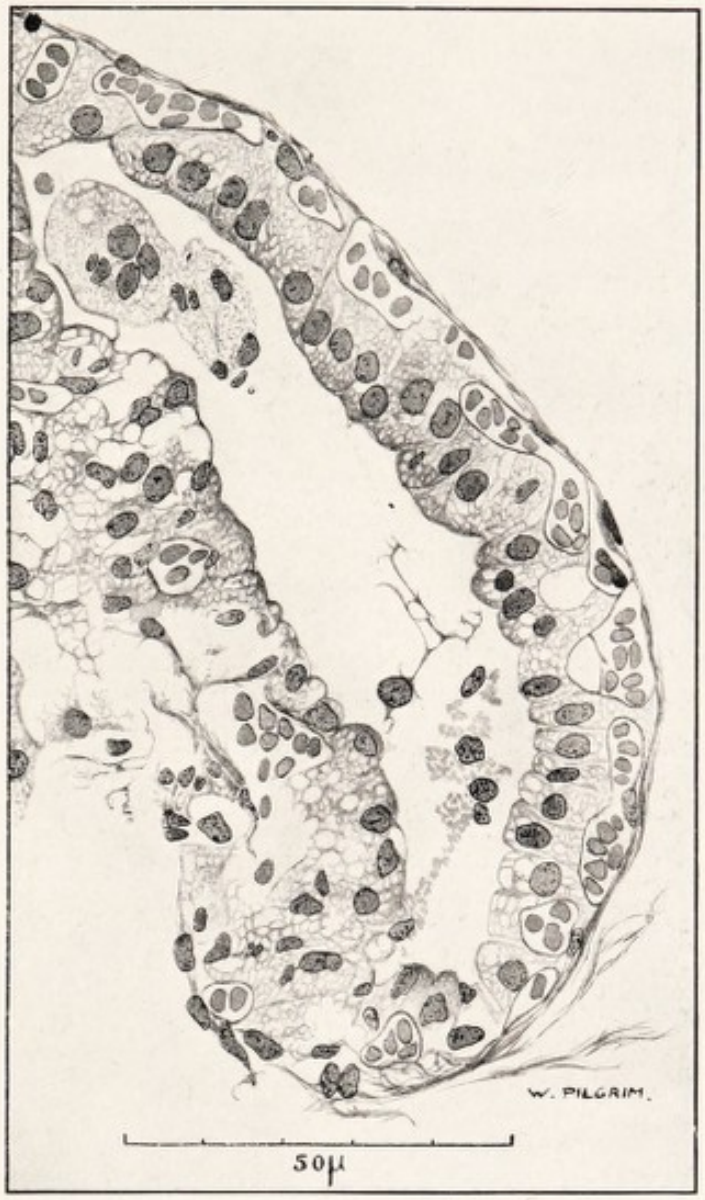

PLATE 18.

Alveolus of thyroid gland from a mouse exposed to cold for three hours. The figure illustrates the intense congestion of the intra-alveolar capillaries which raises the epithelial cells from the basement membrane and leads to desquamation and to the thinning out of some of the epithelial cells to a narrow bridge of protoplasm separating the alveolar lumen from the dilated intra-alveolar capillaries. Formol saline $\times \frac{720}{1}$.

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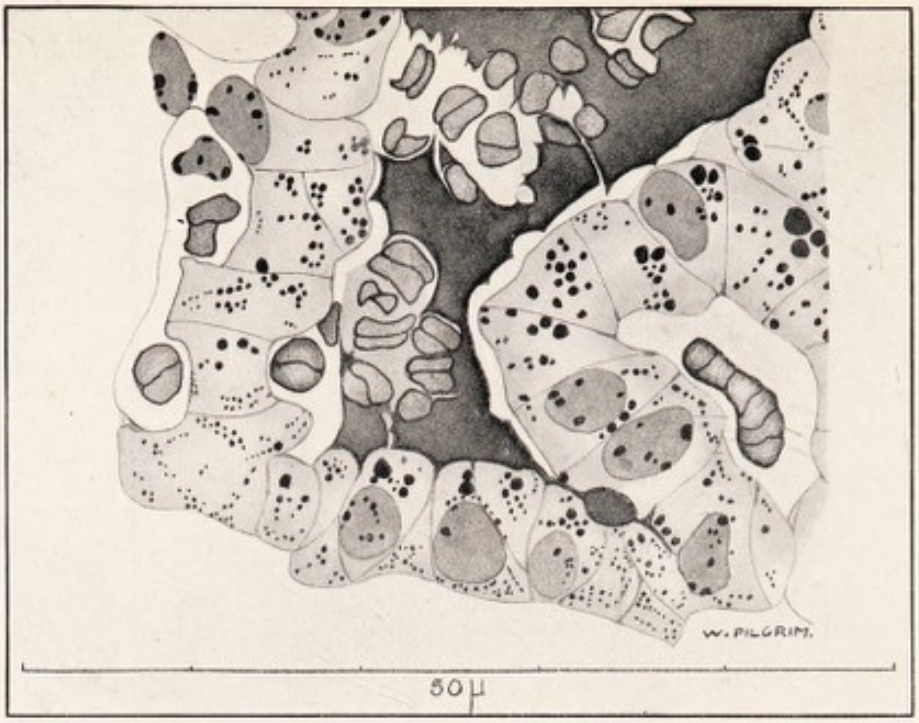

PLATE 19.

Alveolus from thyroid gland of mouse showing dilatation of intra-alveolar capillaries and hæmorrhage into the alveolar lumen. The mitochondria of the epithelial cells are stained. Schridde $\times \frac{1640}{1}$.

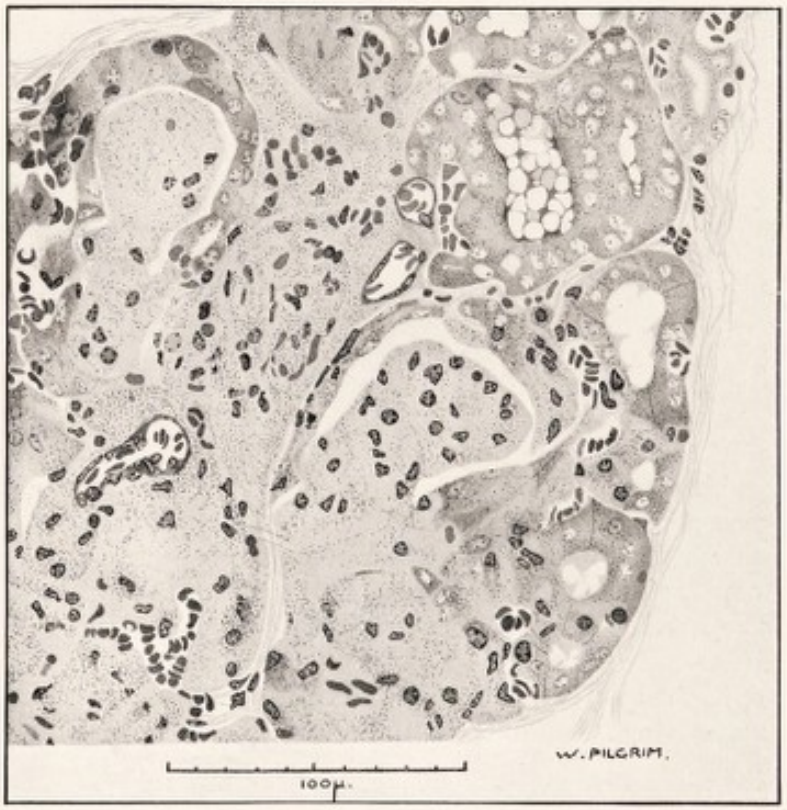

PLATE 20.

Thyroid of rat kept for ten days in cold room at 4° C. Weight and temperature normal when killed. No macroscopic lesions found post mortem. The figure shows several alveoli collapsed and free from colloid, but retaining their normal appearance. Many alveoli, however, as the result of desquamation of epithelium and hæmorrhages into the alveoli, have lost their typical structure. Schridde $\times \frac{280}{1}$.

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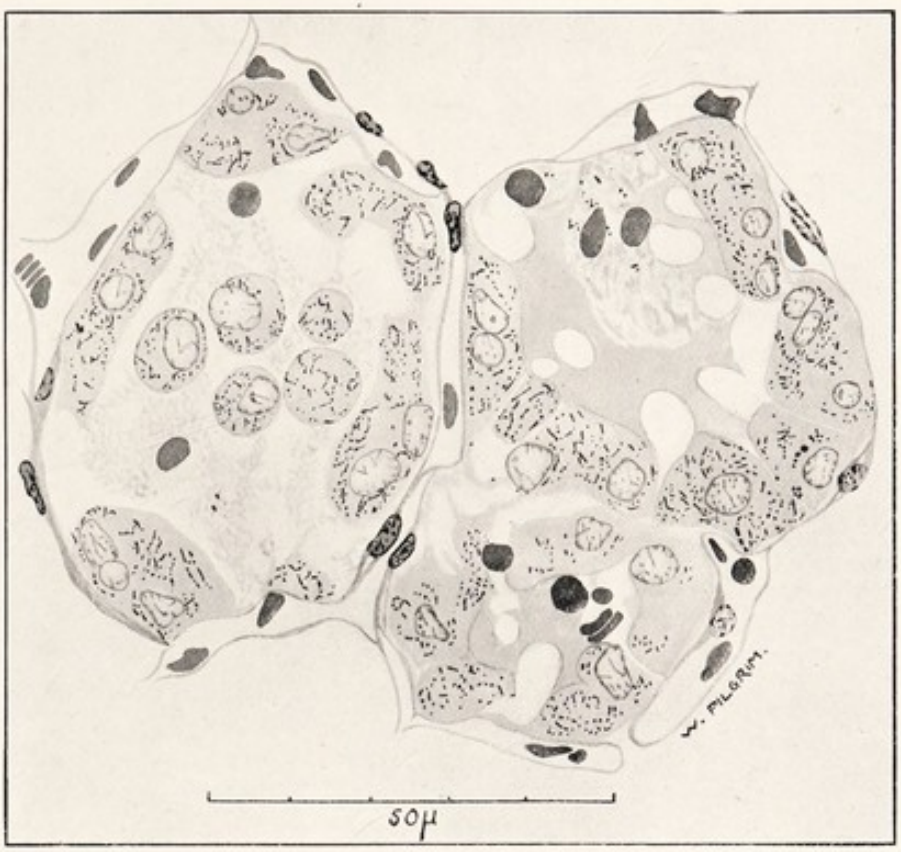

PLATE 21.

Thyroid of rat kept for fourteen days in cold at about 4° C. Temperature and weight of the animal had remained normal, and no macroscopic lesions were found post mortem when the animal was killed with coal gas. The figure shows very extensive disappearance of colloid, small hæmorrhages and recent desquamation of a few cells, in which the mitochondria are still stained. The remaining colloid has a watery consistency and has lost its staining affinity for Heidenhain's hæmatoxylin, which it exhibits in the resting gland. Schridde $\times \frac{760}{1}$.

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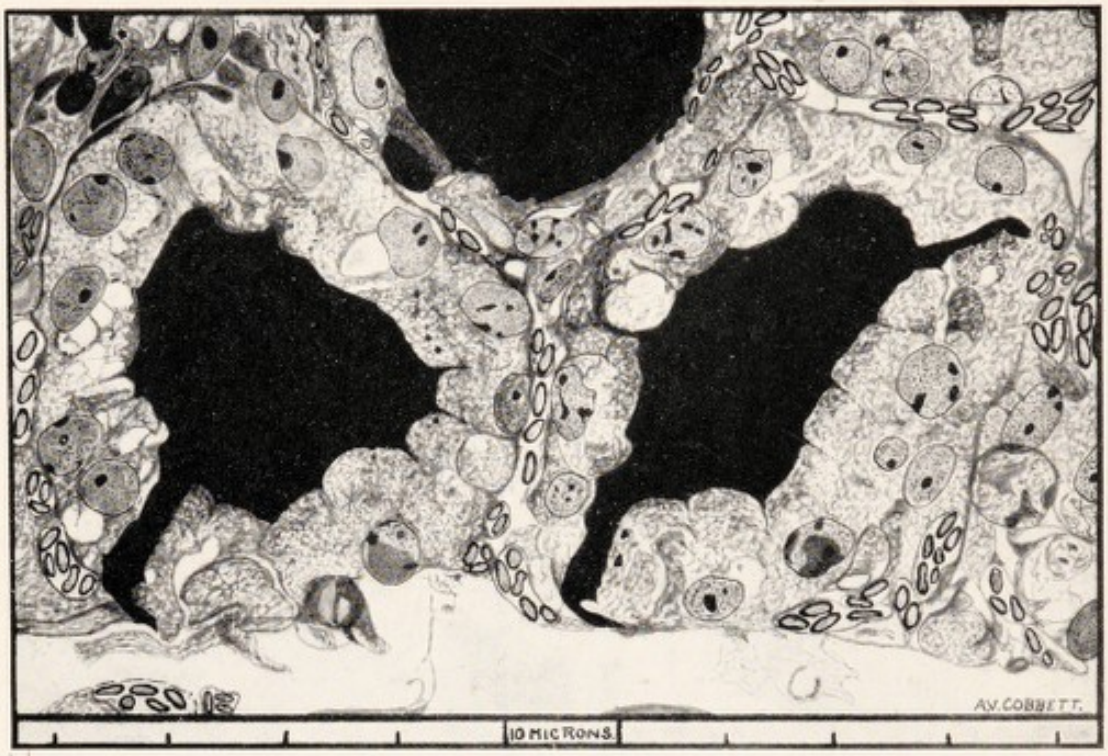

PLATE 22.

Alveoli of thyroid from a rat which had been epilated and exposed to cold for one and a quarter hours and killed with coal gas. The figure illustrates the passage of the darkly stained colloid from the alveolar lumen into the extra-alveolar vascular channels. The appearance in the two lower alveoli suggests that the colloid flows through clefts between the cells. Schridde $\times \frac{1000}{1}$.

CHAPTER VII

SELF-CONTROL AND INHIBITION IN THE ADRENAL GLAND

THE adrenal gland presents a unique problem. The secretion of the gland is under the control of the sympathetic nervous system, which stimulates secretion. The product of secretion—adrenalin—has as its effect stimulation of the sympathetic nervous system. The inactivation of adrenalin by the tissues is so rapid that so long as only very small amounts of adrenalin are secreted all the circulating adrenalin may have disappeared from the blood before it has completed its circulation. But with a more massive secretion the adrenalin cannot be destroyed sufficiently rapidly to prevent it reaching the adrenal again. One would then expect stimulation of the sympathetic nerve endings in the adrenal leading to a further secretion of adrenalin. In other words, once a sufficiently massive secretion of adrenalin is started, the gland by the secretion of its own hormone should continue to stimulate itself. The result would be therefore to transform a slight and short stimulus passing over the sympathetic nervous system into a strong and lasting stimulation of all the organs and tissues innervated by the sympathetic. The function of the adrenal would thus explain itself as that of a "relay station" for the sympathetic nervous system. There is experimental evidence in support of this view. It has been found, for instance, that the so-called sugar piqure produces after adrenalectomy only hyperglycæmia and

not glycosuria as it does in the presence of the adrenals, and Griffith has shown that the various procedures leading to hyperglycæmia are much less effective when the adrenals are excluded.

But this process must be controlled and capable of inhibition. Otherwise a stimulus inducing secretion of adrenalin would initiate a kind of " avalanche phenomenon " in which the gland would continue to stimulate itself with progressively increasing force to complete exhaustion. If we agree with Cannon that anger is accompanied by a secretion of adrenalin we may find an illustration of such a process in the uncontrollable frenzy to which an excitable person may be roused by a comparatively slight stimulus when he " loses his temper ". As a rule " self-control " prevents the occurrence of such an incidence. It is obvious that if such a self-control exists in the adrenal it should manifest itself in the gland after the injection of a fairly large dose of adrenalin, for we know that the direct effect on the circulation of even large doses of adrenalin passes off with extreme rapidity.

The effect of adrenalin on the adrenals is shown in Plates 23 and 24. In a normal mouse the zona fasciculata of the cortex is separated from the medulla by a continuous strip of the zona reticularis (see Plate 1). The line of demarcation of the medulla is sharp, continuous and even. If the gland is examined fifteen to twenty minutes after a fairly large dose of adrenalin, that is to say, long after the obvious effect of adrenalin has passed off, there is a very broad zone separating the zona fasciculata from the medullary cells containing adrenalin, as if the zona reticularis had undergone hypertrophy. Moreover, we find now that the line of demarcation between cortex and medulla is no longer sharp and even. Here and there groups of cells containing adrenalin are jutting out into the *apparently* hypertrophied zona reticularis. We may even find islets of adrenalin-containing cells lying in this zone. The medulla itself is narrower than in the normal

resting gland, even in the centre of the gland where it normally is most massive, so that the *apparent* hypertrophy of the zona reticularis has taken place at the expense of the medulla. Obviously no real hypertrophy can have occurred in the short time which has elapsed since the injection of adrenalin. The changes which have been described, in particular the occurrence of islets of adrenalin containing cells isolated from the medulla, lead one to conclude that adrenalin has disappeared from the peripheral parts of the medulla. When the medullary cells lose their adrenalin they also lose their characteristic morphological appearance, by which we normally distinguish them as medullary cells, and they become not readily distinguishable from cortical cells. The *apparently* hypertrophied zona reticularis is therefore *really* medulla from which the adrenalin has ebbed back, so to speak, with the exception of a few islets. This change is induced more readily in female than in male animals.

We have seen that once the adrenal is stimulated to active secretion it is also stimulated to a rapid new formation of adrenalin. The secretion begins at one pole of the medulla around the central vein and its immediate tributaries, while the process of new formation of adrenalin involves the innermost cells of the true zona reticularis, the cells which are immediately adjacent to the medullary cells. There exists, therefore, in the normal gland a particularly intimate relationship between the medulla and the immediately adjacent cells of the zona reticularis of the cortex. As the result of the injection of adrenalin an entirely new process takes place in the medulla. There is an ebbing back of the specific secretion of the medulla from its peripheral cells so that a zone of adrenalin-free cells is interposed between the cells of the zona reticularis and the central adrenalin-containing cells of the medulla, indicating that the new formation of adrenalin is inhibited and that some controlling factor has come into

play. The formation of such a zone is therefore interpreted as interfering with the interaction of cortex and medulla, which is essential for the normal functional activity of the gland. It is the morphological manifestation of the check which the gland imposes upon itself in this condition, and by which it protects itself against self-exhaustion. We propose to call this phenomenon " self-control " of the adrenal.

The same phenomenon has been observed in another condition, namely, after thyroid feeding over a prolonged period. It was, in fact, first observed several years ago in mice fed with small doses of thyroid over three months, and was then recorded in the accompanying drawings (Plate 25). The adrenalin-free peripheral zone, with occasional islets of cells containing sparse granules of adrenalin, is particularly distinct in this condition. It was possible to demonstrate conclusively that this zone belonged to the medulla and not to the cortex, by discontinuing the thyroid feeding and noticing the behaviour of this zone during the recovery. Plate 26 is taken from the adrenal of such an animal when after feeding for three months with thyroid gland the administration of thyroid had been discontinued for three days; it shows the gradual reappearance of adrenalin granules in the cells of this zone. The gland still shows the broad zone of adrenalin-free medullary cells, but the islets of cells containing adrenalin have become much more numerous. Plate 27 gives a high-power view of this zone, showing here and there cells or cell-groups renewing their load of adrenalin. In some of these cell-groups the granules of adrenalin are exceptionally large.

At the time when these observations on thyroid-fed animals were first made the significance of this process was not clearly understood. Its occurrence after injection of adrenalin has enabled us to interpret it, as stated above, as a mechanism of " self-control " of the gland. The work of Marine and Baumann has given

evidence of a specific relationship existing between the thyroid and the suprarenal cortex. In the light of their work it seems possible that the change produced by thyroid feeding in the adrenal is due partly to an action on the cortex, which then reacts on the medulla.

In many of the thyroid-fed animals the cortex also exhibits a change in the distribution of the lipoid globules. Instead of being situated mainly in the outer half or two-thirds of the cortex — that is, the zona glomerulosa and the outer half of the zona fasciculata, as they are in the normal resting gland—they remain in the cells of the zona glomerulosa but disappear from the outer part of the zona fasciculata. Sometimes the innermost cells of the zona fasciculata are filled with these globules so that a narrow band of lipoid-containing cells surrounds the medulla. But in other cases there is an extensive disappearance of the lipoid from the cortex, except, as already stated, the narrow peripheral zone of the cells of the zona glomerulosa. This cortical change frequently accompanies the medullary change described above as "self-control", but does not always do so and therefore has a different significance. The key to its interpretation is furnished by the following observations, which show that it is the outstanding feature of the change induced in animals exposed to heat. As will be shown, it represents another method of producing inhibition of the functional activity of the gland.

We have seen that the active secretion of the hormones of these two glands increases heat production. Adrenalin by its peripheral vaso-constriction also diminishes heat loss. These two hormones affect, therefore, both the physical and the chemical heat regulation of the body. Exposure to cold, which calls for increased heat production and diminished heat loss, is a powerful stimulus to the functional activity of these glands. Conversely, prolonged functional activity of these glands not due to stimulation by a cold environment produces fever accom-

panied by rigor. It is clear that the regulation of the body temperature through increased functional activity of the thyroid-adrenal apparatus can only be efficient in one direction—namely, in the direction of maintaining the body temperature at a higher level than that of the surrounding environment. If, now, an animal such as the mouse or the rat, which has no sweat glands and cannot increase heat loss through perspiration, is placed in a warm environment having a temperature approaching that of the animal itself, regulation by heat loss is eliminated. Then even a slight activity of the thyroid-adrenal apparatus would, by increasing heat production, necessarily lead to a hyperpyrexia and endanger the life of the animal. It would, in fact, produce heatstroke. Experimentally this condition can be reproduced by the injection of β-tetrahydronaphthylamine into animals kept in different thermal environments. We have shown in an earlier paper (1920) that a slight stimulation of the thyroid-adrenal apparatus by the injection of a dose of β-tetrahydronaphthylamine, so small that it produces not even a rise in temperature if the animal is kept in a cool environment, will produce hyperpyrexial heatstroke if the animals are kept in a moderately warm room, or even if several animals are crowded together in a small cage. Since in a hot environment adrenal activity is likely to endanger the life of the organism, we may expect that the organism will react to exposure to heat by an inhibition of the adrenal gland.

Mice are very sensitive to heat. It is possible to keep them alive for weeks at a temperature of 37°-38° C. The animals remain quite well. But even a slight increase in the temperature beyond 38° C. will kill them, although the external temperature may only be one or two degrees Centrigrade above their body temperature. When one examines osmic vapour preparations of the adrenals of mice kept for several days at 37°-38° C. the medulla frequently shows no obvious change. The cells

are fully loaded with adrenalin granules. Some animals may show the phenomenon of " self-control " just described in which adrenalin disappears from the peripheral cells of the medulla. This change, however, is not always present. But the cortex always shows a distinct change, namely, an extensive disappearance of the lipoid globules. These disappear completely from the zona fasciculata in which they are normally present and only a narrow band of lipoid-containing cells remains in the outermost layer of the zona glomerulosa. At the same time the animals are in an excellent condition of nutrition and show abundant adipose tissue. The glandular adipose tissue in which the adrenal lies embedded is filled with ordinary fat, with the result that its normal brown colour has disappeared and it looks yellow like ordinary adipose tissue. The disappearance of lipoid from the cortex is therefore in striking contrast to the condition in the other deposits of adipose tissue.

The statement made above that the adrenals of mice exposed to heat show sometimes very distinctly the phenomenon of " self-control "—disappearance of adrenalin from the periphery of the medulla—is illustrated in Plate 28. In such cases there is also a disappearance of lipoid from the cortex, but this is not as complete as in animals in which the medulla has retained its normal load. It is known that the presence of lipoid in the cortex is absolutely independent of the nutrition of the animal. For even in complete emaciation the cortex has its normal load of lipoid. The fact that in starvation the cortex retains so tenaciously its lipoid when the insistent demand exhausts all the other deposits of fatty material gives a special significance to the disappearance of lipoid resulting from exposure to heat. Such a complete disappearance of lipoid has been observed so far only in severe pathological conditions leading to the death of the organism — for instance in many severe bacterial infections.

It will be recalled (see Chapter III.) that activity of the gland, such as can be produced, for instance, by exposure to cold, is associated with a spreading of the lipoid from the outer half over the whole cortex—a migration from the periphery of the cortex towards the medulla. Exposure to heat, on the other hand, produces a disappearance of the cortical lipoid. We conclude therefore that *activity*

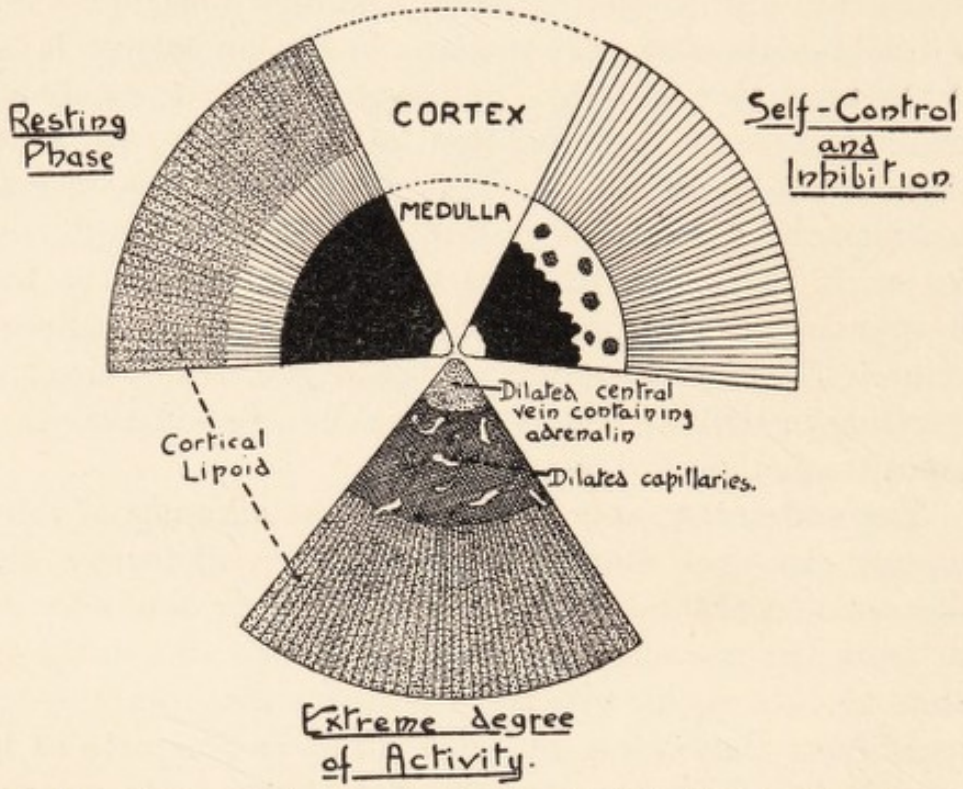

FIG. 11.—Pictographic summary by Dr. R. J. Ludford of the changes in the different parts of the mouse's adrenal gland in the condition of extreme secretory activity and in the conditions described as "self-control" and as "inhibition".

of the gland is accompanied by a spreading of the cortical lipoid over the whole cortex, inhibition of the gland by a disappearance of the cortical lipoid. A pictographic summary of these different conditions is given in Text Figure 11.

The existence of these mechanisms of "self-control" and "inhibition" is of importance in its bearing on the relationship between the thyroid and adrenal gland. The interrelationship of the various endocrine organs and of the thyroid and adrenal in particular has been the

subject of numerous investigations and has given rise to a good deal of controversial writing. It has been suggested by some that the thyroid hormone stimulates the adrenal while others believe that it makes the sympathetic nerve endings more sensitive to adrenalin. A third group of workers deny that any conclusive evidence of any relationship has ever been brought forward and look upon it as "not proven". We do not propose to discuss this subject, which has been fully reviewed in recent books and articles in detail. As happens not infrequently in such controversies the main problem has frequently been lost sight of in attempts to disprove a particular contention, and conclusions have sometimes been drawn which go beyond the facts established by experiment. Thus the fact that sympathetic stimulation, as produced, for instance, by piqure, can elicit an effect in the absence of the adrenals cannot be taken as evidence that in the intact animals the adrenals do not participate. The evidence of Griffith already quoted (see Chapter V. p. 64) indicates that they do. Again, it is not yet conclusively demonstrated whether the thyroid hormone produces its effects by stimulating the adrenal gland directly or by stimulating the sympathetic nerve endings or by just sensitising them. But this much is certain that the adrenal and the thyroid glands are stimulated by the sympathetic, and that hyperactivity of the sympathetic, of the thyroid and of the adrenal produce qualitatively the same effects on metabolism. It is therefore difficult to see how the existence of a relationship between these two glands can be denied, though one may agree that the conceptions which have been put forward in defining their relationship are far too crude.

The fact that adrenalin itself acts both as a stimulus to the adrenal and in another way as a controlling agent shows that this problem of the interrelationship of endocrine organs is much more complex than has hitherto been supposed. When we see that the thyroid hormone has

the same controlling function on the adrenal it becomes evident that the relationship between these glands is one of a delicate and sensitive balance and cannot be discussed adequately in terms of the crude alternative of stimulation or inhibition. The response of the adrenal gland to the thyroid hormone depends partly upon the size of the dose and partly upon the period of time over which it is allowed to act. Large doses of thyroxin or of dried thyroid may produce an active secretion if given over short periods of time. With small doses given over long periods the self-controlling mechanism comes into evidence. Similar relationships exist probably between other endocrine organs.

The existence of these two mechanisms of "self-control" and "inhibition" throws light on some pathological problems of the adrenal. Since the mechanism of "self-control" comes into action by thyroid feeding, *i.e.* in experimental hyperthyroidism, it is likely that the condition of this mechanism may play an important part in clinical hyperthyroidism. Inefficiency of this mechanism may be as important an etiological factor in Graves' disease as the degree of hyperfunction of the thyroid. A degree of thyroid hyperactivity which in a normal organism may produce a condition remaining within physiological limits owing to the efficiency of the mechanism of "self-control" in the adrenal, will produce a greatly exaggerated effect if this mechanism is not efficient. From this point of view the functional condition of the suprarenal may be an important factor in the etiology of Graves' disease. Such a view affords an explanation for many clinical observations in Graves' disease which appear paradoxical and have not so far received a satisfactory explanation. The suggestion that the adrenals become involved in Graves' disease has also been made on clinical grounds by Langdon Brown (1923). He points out that the disordered function of the adrenals may become the predominant factor in the course of the

disease, and may carry it on, so to speak, even when the hyperactivity of the thyroid gland has subsided. It is not suggested here that this occurs in every case of the disease. It is well known that different cases of Graves' disease react very differently to similar treatment—a fact which suggests differences in the underlying condition in different cases. There is also the curiously paradoxical fact that in some cases of Graves' disease adrenalin, or better still the whole adrenal gland given either as such or in form of a glycerine extract (Solis-Cohen, Obregia, Shapiro and Marine, Shapiro), greatly relieves the condition. The effect is puzzling, and contrary to all *a priori* expectations. The demonstration of the mechanism of self-control in the adrenal which can be brought into action by adrenalin offers the solution of this therapeutic puzzle. The same explanation may perhaps apply to the beneficial effects which have been obtained quite recently by the oral administration of iodine (Plummer, 1923; Starr, 1924; Fraser, 1925). This produces in many cases a remission which is as abrupt and as extensive as that following subtotal thyroidectomy. The effect is, however, not permanent, and the disease cannot be cured in this way. If the administration of iodine is stopped the metabolic rate rises again rapidly and the symptoms reappear in a few weeks. It is interesting to note that this therapeutic puzzle was discovered as the result of a mistake in 1863 by Trousseau, who, by a lapse of the pen, prescribed to a patient suffering from Graves' disease tincture of iodine instead of tincture of digitalis. A striking confirmation of the view that the disease is due to a breakdown of the mechanism of self-control in the adrenal leading to an excessive activity of the gland has recently been obtained by examining the adrenals in a case of exophthalmic goitre occurring spontaneously in a mouse. We are indebted to Professor Leonard Hill for this case, who very kindly put the animal at our disposal. The animal showed very marked exophthalmus, the thyroid

was slightly enlarged and, microscopically, showed the changes characteristic of exophthalmic goitre as it occurs in man. The adrenals showed very profound pathological changes which are represented in Plates 29-31. The cortex of both glands contained abundant lipoid. The medulla of one gland was greatly hypertrophied, fully charged with adrenalin, and showed active secretion of adrenalin (Plates 29 and 30). In the peripheral part of the medulla there were numerous cells, each filled with a large globule of fat. These cells formed a ring surrounding the medulla. In the other medulla this ring of cells filled with large fat globules was much more massive and, in fact, almost completely replaced the medulla. Only in the central part of the gland could a few medullary cells be seen (Plate 31). These, however, were almost empty of adrenalin granules. It will be recalled (see Chapter III.) that the immigration of fat and lipoid into the medulla occurs as the result of intense activity of the gland.

The disappearance of the cortical lipoid in response to physiological conditions imposing an inhibition on the activity of the gland gives a clue to the interpretation of this phenomenon under pathological conditions. As already stated, in human post-mortem material it has been observed frequently though not constantly in many virulent bacterial infections. We shall see in the following chapter that it is found in the terminal stage of such experimental infections as gas gangrene, diphtheria and a streptococcal septicæmia. In these conditions there is in addition a depletion of the load of adrenalin from the medulla. The detailed study of the intermediate stages of bacterial infections, as recorded in the next chapter, shows that many bacterial infections stimulate the activity of the gland. Only if the infection is of sufficient virulence does the inhibitory effect manifest itself on the cortex, thus preventing it from carrying out its normal function of assisting the active medulla in recharging itself

with adrenalin. The relation of the gland to bacterial infections will be discussed more fully in that chapter.

Summary.

The adrenal gland possesses the power to control its functional activity in such a way as to prevent the gland from stimulating itself to complete exhaustion. The existence of such a mechanism is necessitated by the fact that the gland is stimulated to secretion by the sympathetic, and secretes as its specific hormone a substance —adrenalin—which itself specifically stimulates the sympathetic. It is shown that the injection of adrenalin and also prolonged feeding with thyroid gland produce characteristic changes in the adrenal medulla, which effect a " self-control " of the gland.

In addition there is a mechanism which effects an " inhibition " of the functional activity of the gland. This mechanism is located in the cortex and manifests itself as a disappearance of the cortical lipoid. It can be most readily demonstrated by exposing an animal to conditions such as a hot environment under which activity of the gland would lead to the death of the animal by heatstroke.

The bearing of these conceptions on the pathology of the adrenal and thyroid and of exophthalmic goitre in particular is briefly discussed.

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PLATE 23.

Adrenal of mouse twenty minutes after the injection of 0·015 mgm. adrenalin. A comparison with Plate 1 shows that the adrenalin granules have disappeared from the peripheral parts of the medulla, which has now a very irregular outline. The whole of the dotted square covers part of the medulla. The figure illustrates the phenomenon of "self-control". $\times \frac{66}{1}$.

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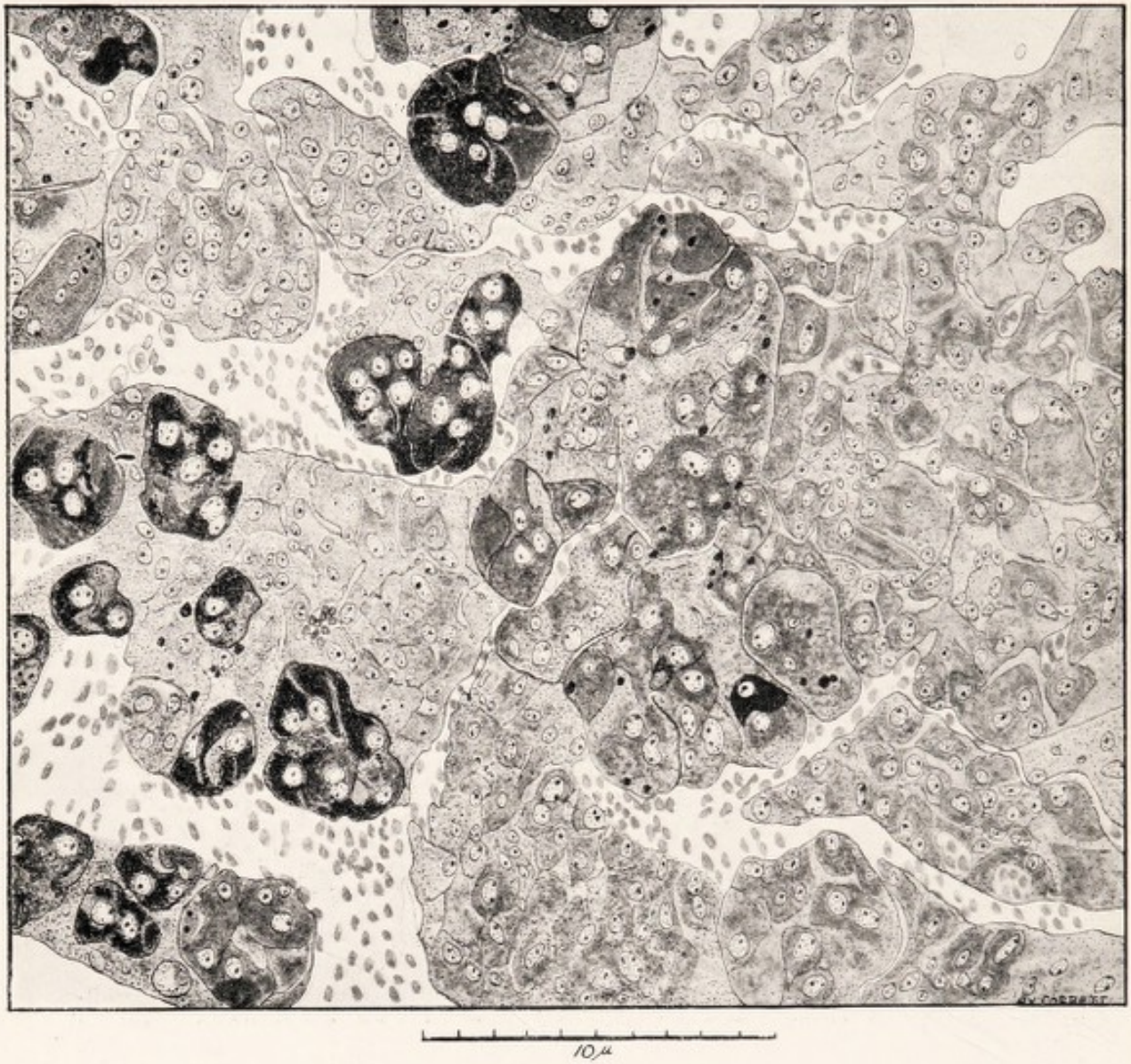

PLATE 24.

High-power view of the area of the medulla enclosed in dotted square shown in Plate 23. Lipoid dissolved by treatment with turpentine. There are still groups of fully charged cells filled with black adrenalin granules and groups of "light" cells with the black "globoid bodies". The greater part of the field, however, is occupied by cells which, while giving no indication of secretory activity, do not contain adrenalin granules and have taken on the external appearance of cortical cells. These cells show a definite arrangement in alveoli similar to that of the fully charged medullary cells. The blood-vessels which are dilated contain no adrenalin granules. $\times \frac{740}{1}$.

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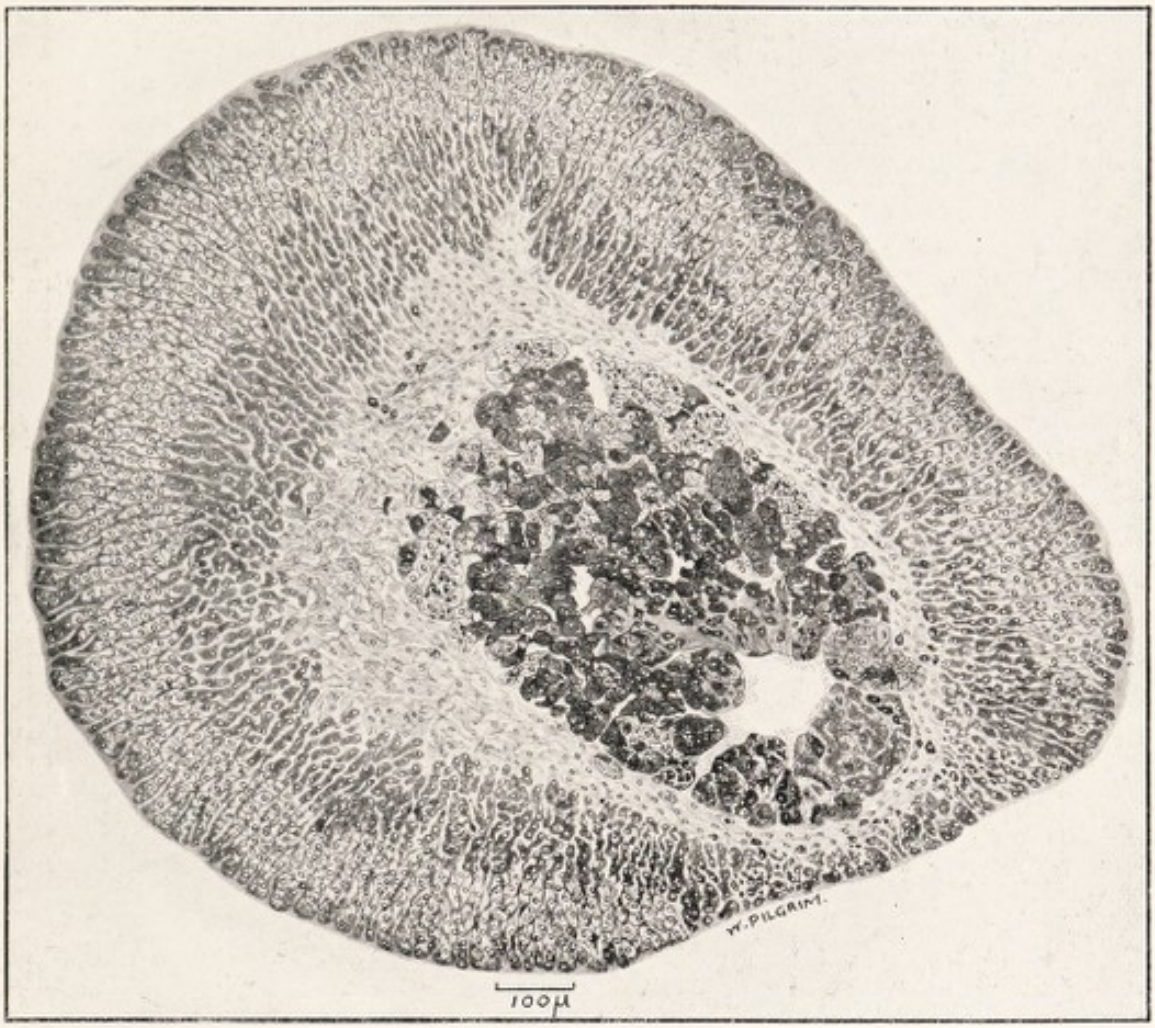

PLATE 25.

Adrenal of mouse fed for three months on small doses of thyroid gland. The gland shows essentially the same change as that found after adrenalin (see Plate 23). Gland has been cut through its short axis. $\times \frac{75}{1}$.

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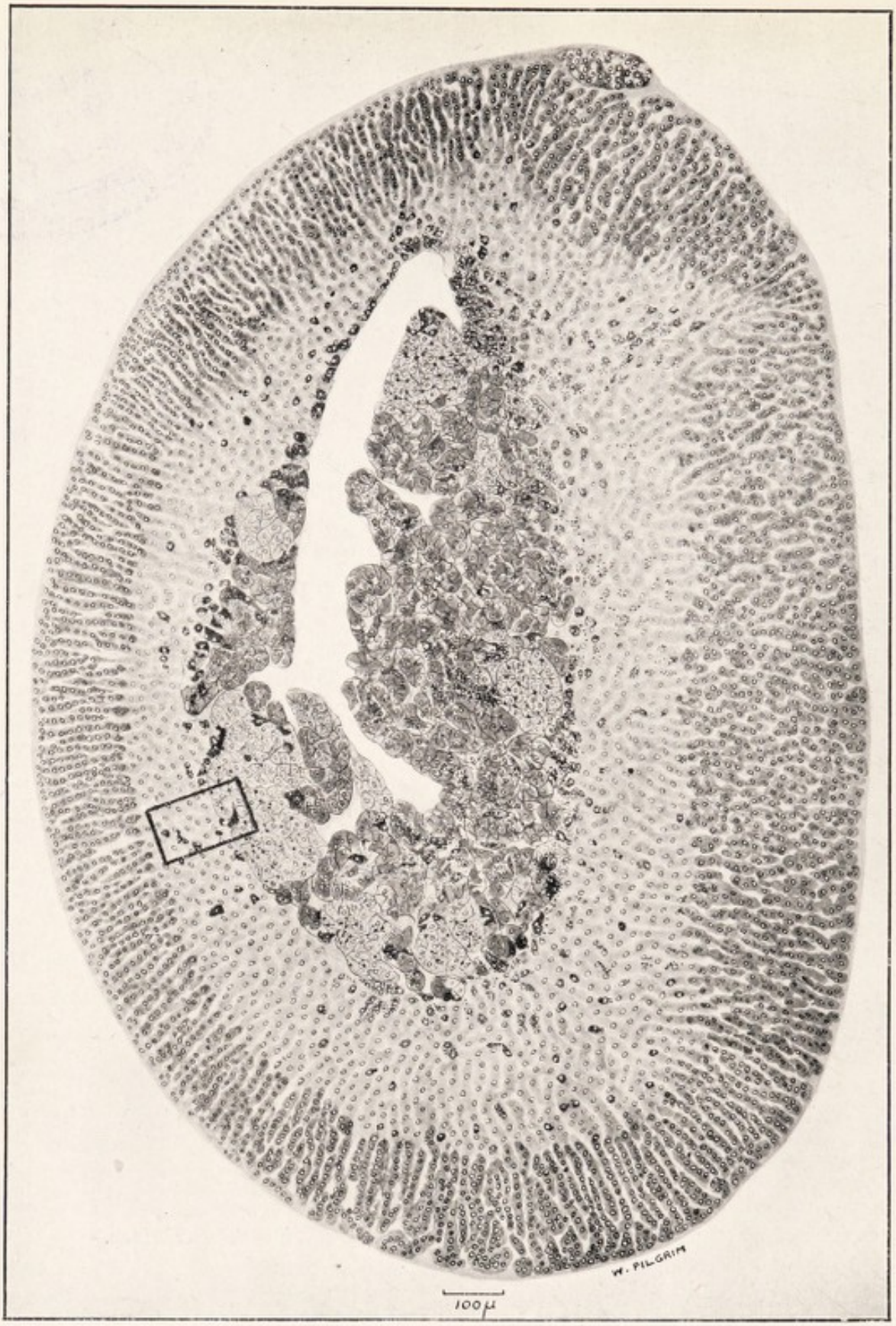

PLATE 26.

Adrenal of another mouse fed for three months on small doses of thyroid gland. Thyroid feeding had been discontinued three days before mouse was killed. The appearance of the gland is similar to that shown in Plate 25, but numerous islets of adrenalin-containing cells are now beginning to appear in the peripheral part of the medulla of which the greater part is still free from adrenalin. The dotted area encloses several islets. The gland has been cut along its long axis. The figure illustrates the gradual recovery from the effects of thyroid feeding. $\times \frac{75}{1}$.

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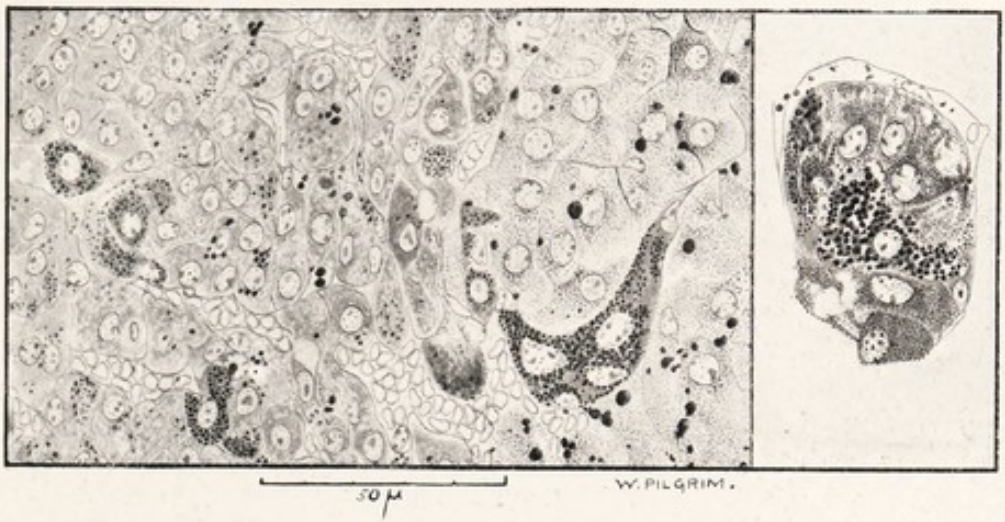

PLATE 27.

High-power view of the area in the peripheral part of the medulla outlined in Plate 26. The lipoid had been dissolved by treatment with turpentine. Shows the gradual reappearance of adrenalin in isolated cells and groups of cells. There is a great difference in the size of the adrenalin granules, some of which are much coarser than the granules seen in the cells of a normal resting gland. The cells containing adrenalin granules lie scattered among cells containing no adrenalin granules, which have superficially the appearance of cortical cells and showing an alveolar arrangement (compare Plate 24). $\times \frac{460}{1}$.

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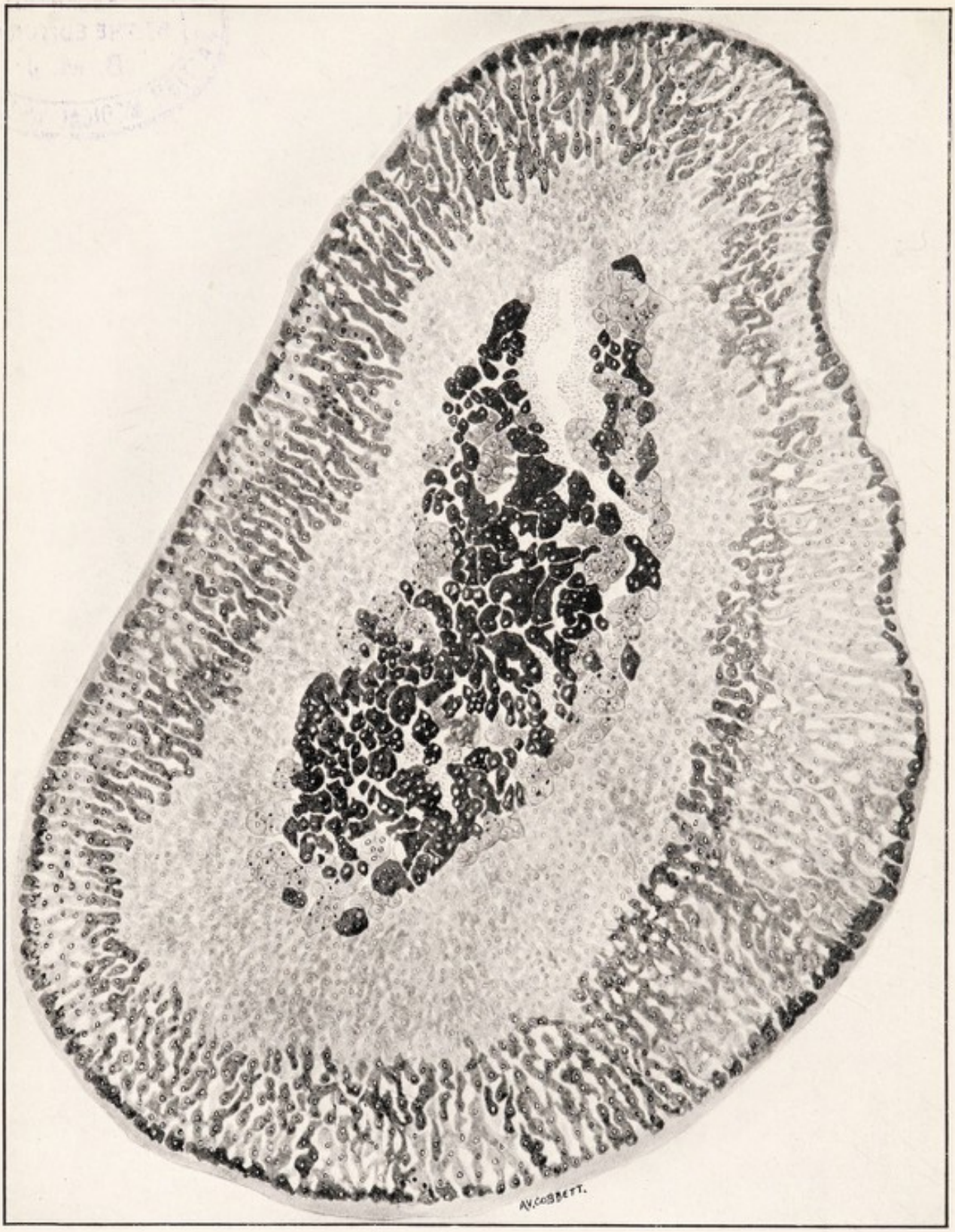

PLATE 28.

Adrenal of mouse kept for two days at 37° C. The figure illustrates an atypical effect of heat, namely, the disappearance of adrenalin from the peripheral parts of the medulla. This is similar to the change observed after adrenalin or after thyroid feeding. There is also a patchy disappearance of the lipoid from the cortex indicated in the figure by differences in shading. $\times \frac{75}{1}$.

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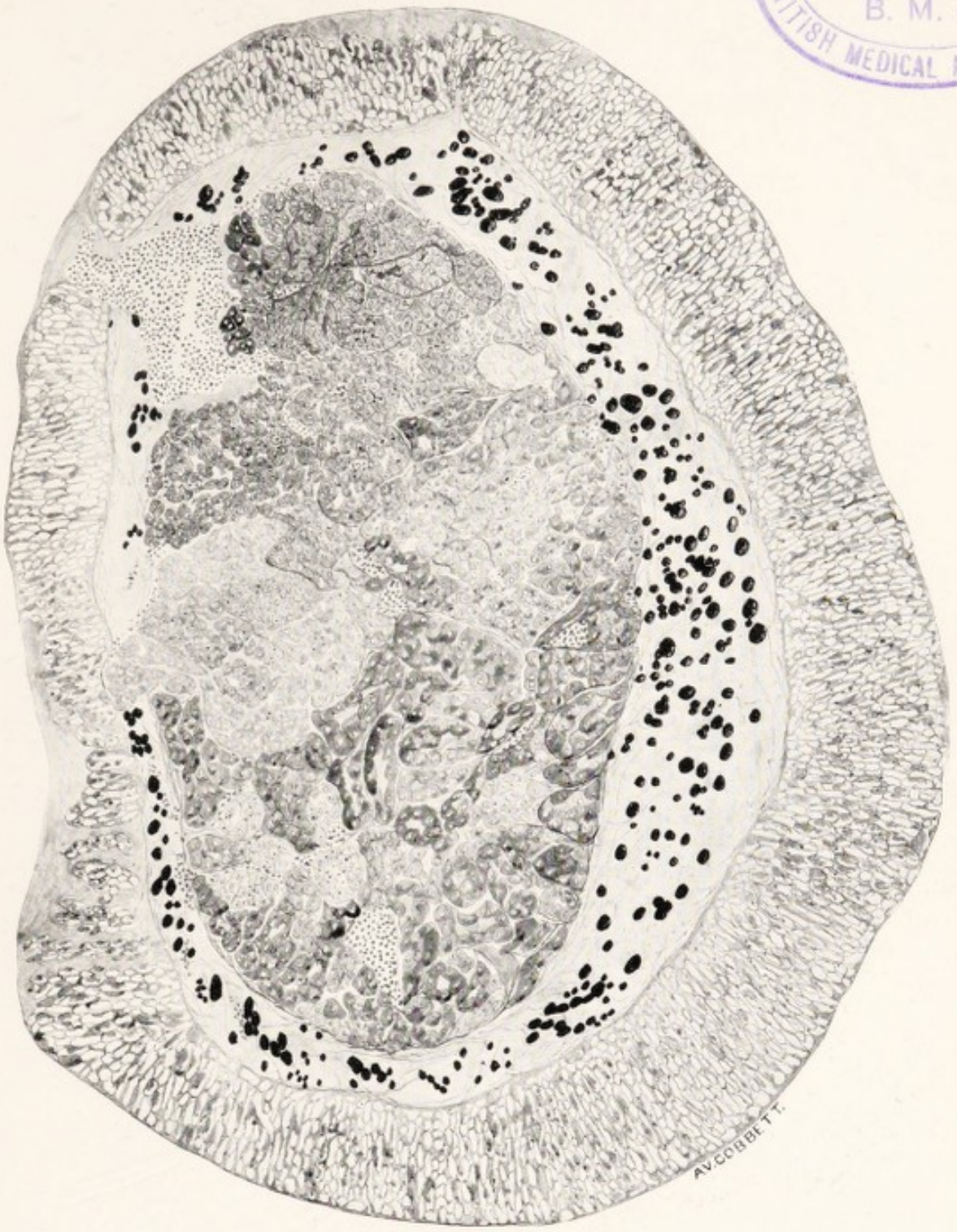

PLATE 29.

One adrenal of mouse with exophthalmic goitre. The medulla is greatly hypertrophied and the medullary cells are fully charged with adrenalin granules and actively secreting. The junction between medulla and cortex is occupied by a ring of cells filled with large globules of fat or lipoid. This appearance is never found in the adrenals of normal mice.

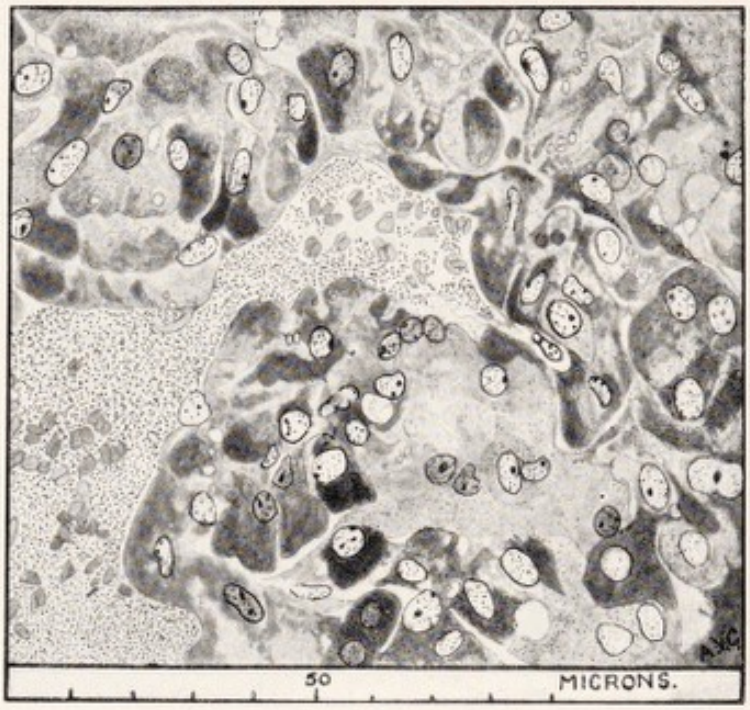

PLATE 30.

High-power view of part of the medulla of the same adrenal showing discharge of adrenalin granules into a blood-vessel and presence of laked cells. The figure illustrates the functional activity of this gland. $\times \frac{600}{1}$.

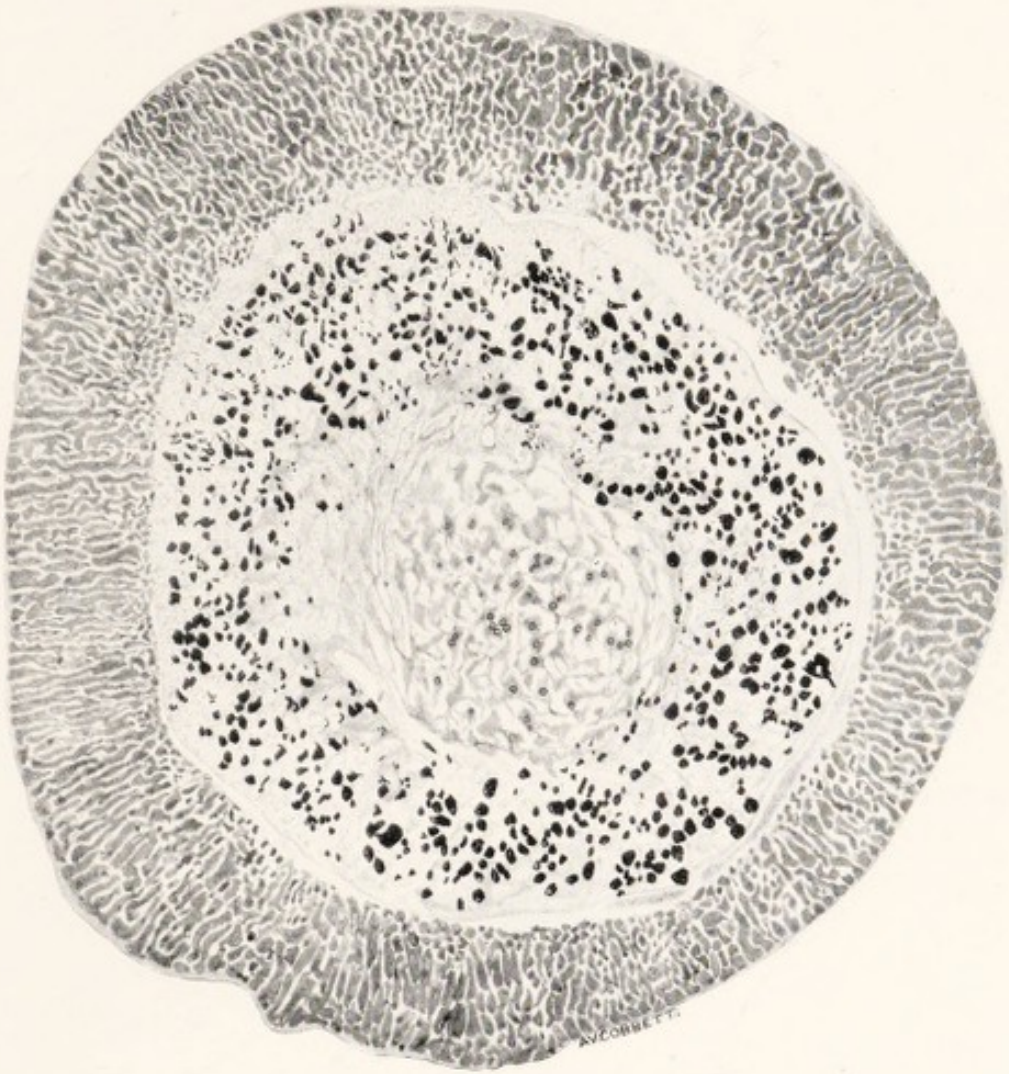

PLATE 31.

The other adrenal of the same mouse with exophthalmic goitre. The section is through the centre of the gland. In this gland the whole medulla has atrophied, only a few groups of degenerated cells almost free from adrenalin remaining in the most central part of the medulla. The medulla is replaced by cells containing large globules of fat or lipoid, similar to those seen in Plate 29 surrounding the hypertrophied medulla. $\times \frac{90}{1}$.

CHAPTER VIII

THE PATHOLOGY OF THE THYROID-ADRENAL APPARATUS

In the preceding chapters we have developed the conception that the thyroid and adrenal glands are endocrine factors in the heat regulation of the body. In the present chapter we propose to deal more fully with the application of this conception to pathological conditions involving disturbances in the heat-regulating mechanism. We may conveniently deal with this pathological aspect under two headings: firstly, those conditions which are primarily diseases of the thyroid and adrenal glands, and secondly, those conditions which are primarily disturbances of the heat-regulating mechanism. The latter are represented mainly by the fevers due to bacterial infections. The condition of the thyroid-adrenal apparatus in Graves' disease has already been discussed in the preceding chapter (see p. 104) in so far as it can be interpreted as a breakdown in the normal mechanism of "self-control" of the adrenal gland.

Heat Regulation in Graves' Disease, Myxœdema and Addison's Disease. The Skin and the Thyroid-Adrenal Apparatus.

It is well known that the heat-regulating mechanism is affected in myxœdema, in Addison's disease, and in Graves' disease. In Graves' disease the increased metabolism of hyperthyroidism and the increased muscular activity (tachycardia, muscular tremor) mean increased heat production; in other words, the chemical heat regulation is stimulated to increased activity. The

physical heat regulation is also stimulated, for the cutaneous blood-vessels are dilated; there is increased perspiration, and respiration is increased. The increased loss of heat resulting from these various disturbances does not always compensate for the increased heat production, so that the temperature may rise above the normal, resulting in periods of actual fever. In fact, clinically, the symptoms of hyperthyroidism may simulate those of early tuberculosis so nearly that attempts have been made to devise special tests in order to distinguish between these two conditions (Goetsch, 1920). We shall see later in dealing with the condition of the thyroid in bacterial infections that this similarity between these two apparently so dissimilar conditions is not an accidental one.

In myxœdema all these conditions are reversed. The chemical heat regulation is depressed as the result of the diminished basal metabolism and the sluggish muscular activity. Instead of the flushed, warm, moist skin of the hyperthyroid patient which promotes heat loss we have the cold, thickened, dry skin with diminished heat loss. The temperature is subnormal.

The deficient functioning of the adrenals in Addison's disease is also accompanied by a subnormal temperature, and subnormal values for the blood sugar in the fasting condition (Rosenow and Jaguttis, 1922), which is associated with and may partly be the cause of muscular asthenia.

These diseases are always associated with characteristic changes in the skin. This follows naturally from the fact that the skin in man plays an important part in heat regulation and that many of its constituent structures (sweat glands, cutaneous blood-vessels, hair) are under the control of the sympathetic and therefore influenced by the thyroid-adrenal apparatus. This may account for the favourable results frequently obtained in certain skin diseases by thyroid medication and for the not infrequent association of trophic changes in the skin with chronic

infections, such as tuberculosis (Pottenger), which affect the thyroid-adrenal apparatus. It is also of interest in this connection that some skin diseases are influenced by a change in the weather. In addition, there is one disease, sclerodermia, in which there is evidence that the disease is frequently associated with disease of the thyroid gland and less frequently with disease of the adrenal. The association is not an obvious one, since sclerodermia has been observed to occur both in Graves' disease and in myxœdema. A very full account of the whole subject is given in a paper by Castle. Quite recently several authors (for literature see Longcope) have recorded in cases of sclerodermia a subnormal basal metabolism and a subnormal blood sugar in the fasting condition. Similar investigations in sclerodermia and other diseases of the skin might yield interesting information on the relationship between the skin and the thyroid-adrenal apparatus.

Adrenal Hæmorrhage and Heat Regulation.

Hyperadrenalism as a primary disease is not recognised as a clinical entity in the same way as hyperthyroidism. This may be due to the fact that the morbid histology of the adrenal presents a much more difficult problem than the thyroid gland. There are, however, on record conditions in which the only lesion found post-mortem is intense congestion of the adrenals with hæmorrhages into the glands. An outstanding symptom which is frequently associated with this condition is a sudden hyperpyrexia, which may occur in the absence of any demonstrable infection, or which is too violent to be accounted for by any infection that may be present. The patient may die in a day or two, the general clinical picture being that of a virulent infection, for which it is frequently mistaken. The hæmorrhage may be visible as such to the naked eye, or it may only be seen on microscopic examination—the naked-eye appearance only showing intense congestion. My limited pathological material includes

two such cases. One was an infant which was admitted to the hospital having developed rapidly a temperature of 104°, and which died a few hours after admission. No evidence of any infection could be found post-mortem. The other case was that of a man, aged 60, who had been operated on for enlarged prostate. The operation was successful, and the temperature remained normal for the succeeding seven days. Then the temperature suddenly rose, and the patient died on the following day. It was suspected that an infection had supervened, but no evidence of this could be found at the post-mortem examination. In both cases the zona reticularis and the medulla of the adrenals showed intense congestion with diffuse hæmorrhage into the medulla.

This condition of diffuse adrenal hæmorrhage associated with congestion is perhaps more frequent than the relatively few number of cases recorded in the literature indicate. It is rarely, if ever, diagnosed during life. The adrenal is not always examined carefully at autopsies, and unless the hæmorrhage is visible to the naked eye it would be missed. Sometimes the fever may subside and be followed by a subnormal temperature and asthenia, so that the patient dies with the symptoms of adrenal insufficiency. Such a case in which post-mortem a large macroscopic hæmorrhage into the adrenals was found has been described by Hektoen (1910). The patient had been operated on for an inguinal hernia. The temperature remained normal for three days after the operation, then rose to 102° ; it then became normal until shortly before death, fourteen days after the operation, when it fell below normal. The history of this case suggests that the initial stimulation of the gland was followed by a slow hæmorrhage into it which gradually destroyed the medulla. Severn (1923) records an instructive case of acute bilateral suprarenal hæmorrhage which simulated an acute infection in its symptoms : a pyrexia of 102°, a rapid pulse of 126, and cold face and extremities, followed

by collapse. Another group of cases is distinguished by the occurrence of purpuric eruptions (Graham Little, 1901), either with or without a rise in temperature. In the former group of cases death ensues frequently in a few days. Such cases have often been recorded as purpuric smallpox or hæmorrhagic scarlatina. Dudgeon (1904), however, has pointed out that in many of these cases there has been no clear evidence that the patients had either smallpox or scarlatina, and he suggests that they may have been cases of adrenal hæmorrhage pure and simple unaccompanied by any infections.

Most cases of adrenal hæmorrhage in adults recorded in the literature refer to large hæmorrhages visible to the naked eye, to which the name " adrenal apoplexy " has been applied by some authors. A systematic microscopic investigation of the adrenal would probably show a considerable number of cases of diffuse hæmorrhages which have so far escaped detection. From a study of the cases recorded in the literature it is clear that adrenal hæmorrhage may be the result of a variety of causes. Thrombosis of the adrenal vein is a frequent cause. Disease of the blood-vessels due, for instance, to syphilis is another predisposing cause. An instructive case of this kind may be given in which a man, aged 40, with a history of syphilis and suffering from pyorrhœa, developed a temperature of 102·5° and a pulse of 120. Post-mortem examination showed hæmorrhage into the adrenal with thrombosis of the adrenal vein. Destructive disease of the gland may also conceivably lead to a hæmorrhage into the gland. Another cause is the action of a toxin on the endothelial lining of the capillary spaces in the gland, especially when it is associated with the dilatation of these spaces, and the congestion of the gland which, as will be shown presently, accompanies many of the bacterial infections. One of the earliest cases recorded in the literature is that of a man, aged 29, who died of pneumonia (Greenhow, 1877). Post-mortem examination

revealed a hæmorrhage in the suprarenals. Of the numerous cases collected by Arnaud, two were observed as having occurred after extensive burns, while one was found in a person frozen to death ("coup de froid"). The paper by Arnaud (1900) gives a very complete collection of all cases recorded in the literature up to 1900. Since then a number of other cases have been reported, in addition to those mentioned above (Pritchard, 1890; Simmonds, 1902; Dudgeon, 1904; Lissauer, 1908; Lavenson, 1900; Brodnitz, 1910; Goldzieher, 1911; Freudemann, 1920; Michaux and Marsset, 1923).

Of particular interest is the occurrence of hæmorrhages in the adrenals which has been observed in malaria (Paisseau and Lemaire, 1916; Dudgeon and Clarke, 1917) and in influenza (Winter, 1918; Wolbach, 1919)—two conditions which are particularly associated with an intense hyperthermia of the type which, from our experimental observations, one would expect to be associated with great activity of the suprarenals. Generally speaking, therefore, adrenal hæmorrhage is particularly apt to occur in certain bacterial infections which involve intense stimulation of the gland. In these cases the pyrexia could be accounted for as a symptom of the bacterial infection. But, as has been stated above, there are cases of adrenal hæmorrhage which have been preceded by a pyrexia developing suddenly in the absence of a demonstrable infection. In such cases the pyrexia may in the light of our experimental observation be attributed to a sudden hyperæmia of the adrenals due to some intrinsic cause; it is an "aseptic fever". This accounts, as we shall see presently, for the frequent occurrence of adrenal hæmorrhage in the new-born. The abnormal production of a substance, which, like β-tetrahydronaphthylamine, has a strong stimulating action on the adrenals, must be considered as a possibility in some cases. We know from the work of Barger and Dale (1910), on sympatho-mimetic amines, that intestinal

putrefaction may produce from the amino-acids of proteins amines having a powerful action on the sympathetic system.

It is curious that of the relatively few cases of adrenal hæmorrhage recorded in the literature, a great many refer to babies soon after birth (Still, 1897 ; Garrod and Drysdale, 1897 ; Arnaud, 1900 ; Hamill, 1901 ; Dudgeon, 1904 ; Litzenberg and White, 1908 ; Friederichsen, 1918 ; Rabinowitz, 1923). This prevalence apparently has led to the belief that this condition is due to mechanical injuries received at birth. It is difficult to see why the adrenal of all organs should be liable to such injuries at birth. The importance of the adrenal gland as an endocrine factor in heat regulation offers a more satisfactory explanation. As long as the fœtus is *in utero* no call is made on the heat-regulating mechanism. But such a demand is suddenly made at birth, and during the first few weeks after birth an extraordinary process of involution of that part of the fœtal adrenal which lies between the medulla and the permanent cortex transforms the adrenal of the human fœtus into that of the typical gland. This process, which will be discussed in detail in the following chapter, is accompanied by an intense congestion, particularly at the junction of medulla and cortex, for which the sudden change in the thermal environment at and after birth is probably the stimulus. It is easy to see how this normal process may be carried too far and lead to a hæmorrhage into the adrenals. The clinical observations of both Friederichsen (1918) and of Corcoran and Strauss (1924) show also that one of the symptoms of adrenal hæmorrhage is fever. In the case of a new-born baby, which the latter authors report, the temperature rose to 105° F. on the fourth day after birth. A hæmatoma was removed from the adrenal. This was followed by complete recovery. In this case there was no evidence of an infection, but in some of the cases reported in the literature the hæmorrhage must be attributed to a concurrent infection.

These clinical and pathological observations may be summarised as showing that adrenal hæmorrhages are almost always accompanied by a sudden fever, in which the patient may die. It may even be accompanied by purpuric eruptions. Sometimes the fever subsides, and is followed by asthenia or collapse with a subnormal temperature. Adrenal hæmorrhage is a lesion which may occur in the course of bacterial infections ; it has also been found in the absence of such infections. In the latter case the fever may be described as an " aseptic fever ". What, then, is the relation of such an " aseptic fever " to the " septic fevers " of bacterial infections ? Is the underlying process the same, and related in both conditions to an increased activity of the adrenal leading to congestion and hæmorrhage ? Or are the two processes fundamentally different, and is the similarity of the adrenal lesion merely an accident which has no significance ?

Septic and Aseptic Fevers : Similarity of Metabolic Changes in Malarial Fever and in Sympathetic Fever.

It has been held by some writers that the processes underlying the fevers due to bacterial infections are fundamentally different from the aseptic fevers, but are essentially similar in the various bacterial infections. On this assumption the various bacterial toxins are supposed to act in an essentially similar manner on the heat-regulating mechanism. This *a priori* conception of an essential similarity of the mechanism underlying the different " septic " fevers and of a fundamental distinction between them and the aseptic fevers seems to us ill-founded. For the several types of fevers produced by various bacterial toxins differ as widely from each other as they differ from the aseptic fevers. The hectic type of fever in tuberculosis and the rigor of malaria or of an acute streptococcal infection represent two very different types of disturbance of the heat-regulating

mechanism. The same difference in type exists in aseptic fevers produced in different ways: the hyperpyrexia elicited by the injection of β-tetrahydronaphthylamine corresponds to the malarial rigor, while prolonged thyroid feeding produces an entirely different type of fever (Chapter IV. p. 51), resembling the hectic type of tubercular infections. There are, moreover, bacterial infections such as diphtheria or gas gangrene in which, after an initial fever, the course of the infection may be accompanied by a subnormal temperature. Again, observations on the metabolism in fever have failed to produce any convincing evidence that the chemical heat regulation in bacterial infection is fundamentally different from that of the normal organism.

The complete calorimetric investigation of fevers in man presents obvious technical difficulties, and most investigations deal only with isolated aspects of the metabolism of fever. Great credit is due to the workers in the Russel Sage Institute of Pathology in New York for having overcome these difficulties by the construction of a respiration calorimeter capable of measuring the rapid and irregular metabolic changes occurring in fever. Among other fevers they have investigated the metabolism in malaria (Barr and Dubois, 1918). This is of special interest, as the different phases of a malarial attack exhibit many different types of fever. Their results are briefly as follows: During the chill, when the rectal temperature rises abruptly, the heat production is rapidly increased 100 to 200 per cent. In spite of this rapid increase the heat elimination, however, is not increased, nor is the surface temperature, which may actually show a fall. After the chill the surface becomes warmer, the heat elimination increases slowly until it equals the heat production, so that the temperature remains high. With the onset of sweating the heat loss is enormously increased and exceeds heat production so that the temperature falls. After the attack both heat

production and heat loss return to the normal. The respiratory quotient is higher during the chill than before or immediately after it, indicating an increased oxidation of carbohydrates. The nitrogen excretion is increased during the attack in spite of an ample intake of food, and in two cases this increase persisted for several days after the attack. A constriction of the peripheral blood-vessels during the chill was demonstrated long ago in 1888 by Maragliano by means of the plethysmograph. It is interesting to note that this constriction begins actually before the chill, and that similarly the rise in the respiratory quotient sets in before the chill.

It will be seen that all the metabolic features of malarial fever during the chill are a replica of those found in experimental "sympathetic fever" after the injection of β-tetrahydronaphthylamine. Even the persistent increase in the nitrogen excretion occurs in the latter condition. It is, as we have seen (Chapter VI.), the result of the increased activity of the glycogenic function, and need not be attributed to a *toxic* protein destruction. These very complete observations indicate that the fever of a malarial paroxysm involves the same mechanism which is set in action when an animal is exposed to cold or when sympathetic fever is produced experimentally. It is not suggested here that all bacterial toxins produce fever in the same way. Some may do so by a peripheral action on the blood-vessels, on the sweat-glands, or by inducing abnormal metabolic processes. We may gain further evidence on this question whether the thyroid and adrenal glands are involved in the various types of bacterial infections by studying the appearance of these glands in different infections.

Adrenal Gland in Bacterial Infections.

The most convincing evidence is obtained from experimental infections, since in human material obtained post mortem the actual cause of death may be some

accessory or accidental factor which has arisen in the course of the infection, and which may itself produce an effect on the thyroid or adrenal glands, and thus obscure the changes due to the bacterial infection itself. For this reason the changes produced by acute infections which have led rapidly to a fatal issue are of special value when dealing with human material.

It has already been shown in Chapter III. (p. 26) that injections in mice of a freshly prepared bacterial vaccine produce an active secretion of adrenalin, and figures illustrating this effect are given there (Plates 6 and 7). Preparations illustrating this effect have been repeatedly demonstrated, at meetings of the Physiological Society in London in 1918, in Leyden in 1926 and at the International Physiological Congress in Edinburgh in 1923. The results are, however, variable. Constant results were obtained by the injection of certain bacterial toxins and by studying the adrenals of mice in which bacterial infections had been induced experimentally. There are two bacterial toxins which can be shown experimentally to produce an exhaustion of the suprarenal gland—diphtheria toxin, and the toxin of *B. Welchii* of gas gangrene (Plate 32). The similarity in this "adrenalotoxic" action is reflected in the similarity of the temperature reaction in the course of these two infections. After a brief initial fever the temperature falls and becomes subnormal, especially if the issue is fatal. It is a remarkable fact that mice, while very susceptible to the toxin of *B. Welchii*, are absolutely resistant to diphtheria toxin. A dose of diphtheria toxin which would kill one hundred guinea-pigs can be injected into a mouse without producing any obvious effects on the animal, and, what is equally remarkable, without producing any change in their suprarenals. This fact suggests that the reaction of the adrenal gland to diphtheria toxin is an important factor in determining the effect of the toxin on the animal as a whole. In other words, the pathogenic effect of the diphtheria bacillus

is dependent, in part at any rate, on the susceptibility of the adrenal gland to its toxin. Lusena, 1903, has stated, in fact, that rats which are usually resistant to the action of diphtheria toxin became susceptible to it after removal of the adrenals. This view is further confirmed by observations made with the toxin of *B. Welchii*. It could be shown experimentally (Bullock (Gye) and Cramer, 1919) that a sublethal dose of this toxin could have a lethal effect in mice if the animals were subjected at the same time to conditions such as exposure to cold, which impose an additional strain upon the adrenals.

The toxin of *B. Welchii* affects not only the medulla, where the adrenalin disappears from the cells, but also the cortex, from which the lipoid disappears almost completely. In addition there is congestion of the gland. Diphtheria toxin produces in the guinea-pig adrenal congestion, with small hæmorrhages in the medulla. The cortex shows a disappearance of the lipoid.

Infection by yet another type of bacteria has been studied by us experimentally, namely streptococcal infections of varying degrees of virulence. Both the strains used when injected by themselves produced a localised abscess and a rise of temperature, without, however, killing the animals. The adrenals showed an active secretion of adrenalin, but with the more virulent strain the medulla secreted more actively so that it was partially depleted. In both conditions the cortical lipoid had not disappeared.

The conditions were varied further in such a way as to induce a streptococcal cellulitis by injecting an ionisable calcium salt together with the bacteria, and thus producing the phenomenon " kataphylaxis " or " defence-rupture ". This eventually led to a streptococcal septicæmia, and with the more virulent strain killed the animals within four days in a condition of collapse. In these animals the medulla was found to be completely exhausted, and the lipoid had disappeared from the cortex. The

gland in fact resembled in appearance those of animals which had died from the effects of gas gangrene toxin. The septicæmia resulting from the less virulent strain did not kill the animals within four days, although they were obviously ill, and in these mice the adrenals were not exhausted ; the medulla showed active secretion and the cortical lipoid was not obviously diminished.

The literature contains several statements (Goldzieher, 1911 ; Weltmann, 1913 ; Elliot 1914) describing similar profound changes in the adrenals in experimental infections with other bacteria (anthrax, pneumococcus, plague, staphylococci, streptococci, Shiga bacillus, typhoid). The results of the various authors may be summarised by saying that experimental infections so virulent or so massive that they lead to death in a few days produce, if the infection is allowed to run its course, a disappearance of the cortical lipoids together with a depletion of adrenalin from the medulla. But if intermediate stages of these infections are examined, the cortical lipoid is found to be increased and to have spread over the cortex. A particularly intense hyperæmia with hæmorrhages has been observed in experimental infections with the pneumococcus. It is of interest to note that even the toxins of intestinal worms (*Ascaris, Tænia*) have been found to produce a disappearance of the cortical lipoid (Bedson, 1913). An interesting confirmation is to be found in the experimental observation that some bacteria produce a rapid hyperglycæmia, with a rapid return to the normal in a few hours and other evidence of sympathetic stimulation (Zeckwer and Goodell, 1925 ; Levine and Kolan, 1926). This rise in blood sugar does not occur in rabbits in which one adrenal has been removed and the other has been denervated (Evans and Zeckwer). There is then a fall of blood sugar. Ergotamine and insulin inhibit the hyperglycæmia. The following bacteria were found to produce a rise in blood sugar: *B. coli, B. proteus, B. paratyphosus, B. dysenteriæ. Staphylococcus*

pyogenes aureus and *Streptococcus hæmolyticus* produced a fall of blood sugar. A third group was without effect on blood sugar. In man the observations of Labbé and Boulin (1925) showed a definitely raised fasting blood sugar, and prolonged blood-sugar curves after the administration of 50 gm. of glucose in such infections as typhoid, pneumonia, erysipelas. Similar results were obtained by Berg in cases of tuberculosis. Euler has brought evidence by an entirely different method for the presence of an increased amount of adrenalin in the serum of fever patients. After having demonstrated in such sera the presence of vaso-constricting substances by means of the Trendelenberg frog preparation, he studied the effect of the sera of fever patients on tissue oxidation as measured by Thunberg's methylene blue method. Based on Ahlgren's findings that adrenalin favours this reaction in a characteristic manner, Euler could demonstrate this favouring effect in the sera of patients suffering from tuberculosis and broncho-pneumonia, and also in the serum of a rabbit in which hyperthermia had been induced by heat piqure. Euler has attempted to give an approximate estimate of the degree of the adrenalinæmia in fever. Normal human serum is estimated by him to contain adrenalin in a dilution of 1 : 10 milliards, while the fever sera examined by him contained adrenalin in dilutions varying 1 : 500 millions to 1 : 1 milliard.

The conclusions which one may draw from all these observations are that the adrenal gland is particularly susceptible to the action of many bacterial toxins. Small doses of many bacterial toxins stimulate the gland to increased activity, while in lethal doses they exhaust the gland. One might describe these effects as " adrenalotonic " and " adrenalotoxic " respectively. There are toxins in which the adrenalotoxic effect predominates. But even a toxin giving an adrenalotonic effect, if its action is sufficiently powerful and prolonged, may eventually lead to an exhaustion of the gland.

For those infections that have an action on the adrenals, there is therefore some evidence that what is vaguely described as their " virulence " is determined, in part at any rate, by their action on the adrenals, and that the exhaustion of the adrenals is an important factor in the lethal issue, which is usually ascribed vaguely to a failure of the circulation. It is hardly necessary to add that there are bacterial toxins, of which tetanus toxin is an example, which produce their toxic action in quite a different manner, or that those infections that have an adrenalo-toxic effect may also have toxic effects on other organs.

The observations also give important information on what constitutes exhaustion of the adrenal gland. It is not merely depletion of the load of adrenalin from the medulla. For this may be brought about by an increased secretory activity of the gland, as, for instance, by exposure to cold or by a dose of β-tetrahydronaphthylamine. If, for instance, after a severe exposure to cold the animal is kept warm it recovers its normal body temperature, and the adrenal medulla fills itself again with adrenalin. And after a dose of β-tetrahydronaphthylamine sufficient to deplete profoundly the load of adrenalin, the body temperature does not fall below the normal after it has recovered from the period of pyrexia, and the medulla assumes its normal load of adrenalin. In the bacterial infections which have been studied experimentally by us, those that lead to the death of the animal in a state of collapse with a greatly subnormal temperature show a depletion of adrenalin from the medulla which is always accompanied by a disappearance of lipoid from the cortex. As shown in the preceding Chapter, the presence of lipoid in the cortex is essential for the proper functioning of the medulla. In its absence the rapid new formation of adrenalin which normally accompanies the active secretion of adrenalin appears to be impaired, so that a condition of adrenal exhaustion or

adrenal insufficiency is produced. Its visible manifestation is the absence of lipoid from the cortex and of adrenalin from the medulla. Such a condition of the gland seems to be incompatible with life.

If one examines intermediate stages in the action of these adrenalotoxic toxins, one finds the lipoids spreading first from the outer cells of the zona fasciculata of the cortex over the whole cortex, and appearing in the inner cells of this zone and in the cells of the zona reticularis, which are normally free from it. There is thus a movement of the lipoid from the periphery towards the medulla, but not as a rule into the medulla itself.

If we turn again to the evidence to be obtained from human pathology, we must realise that the interpretation of observations based on post-mortem material is necessarily much more difficult, and the results must be expected to be less uniform. We cannot study on this material the results of bacterial infections as such. The material which is available is the result of bacterial infections, which were either so virulent and acute that they led to the death of the patient uncomplicated by other factors, or in which the death of the patient was due to some accident or complication, such as a hæmorrhage, nervous paralysis in diphtheria, thrombosis and embolism, etc. In the latter group the accident of death has interrupted the effect of the infection itself on the adrenal or thyroid glands, so that this group corresponds to the intermediate stages of bacterial infections where the animal has been killed before the infection has run its course. For this reason material from acute infections which have led rapidly to a fatal issue are of special value as being capable of a simple interpretation. But one must bear in mind that such material shows only the results which are common to bacterial infections of great virulence, and one must guard against attributing conclusions to any specific bacterial infection.

There is the further difficulty that the medulla of the

suprarenal gland is so particularly sensitive to post-mortem changes, that unless the gland has been obtained in the first few hours after death it is impossible to draw reliable conclusions from the histological condition or the adrenalin content of the medullary cells. The data concerning the load of the normal human medulla vary, moreover, within very wide limits. We must conclude either that post-mortem changes affect the adrenalin content to an even greater extent than is at present admitted, or that in man the size of the medulla and its load of adrenalin is subject to great variations.

Very extensive and careful series of observations on the human adrenal have been made by Goldzieher (1911), T. R. Elliott (1914) and by Weltmann (1913). Goldzieher directed his attention to the hyperæmia and to the load of adrenalin, which he estimated by a quantitative determination of the adrenalin content. Elliott's observations show that the cortical lipoid disappears in acute infections if death occurs as the direct result of an acute febrile infection such as measles, scarlet fever, tuberculosis, diphtheria, malignant endocarditis or pneumonia. But in chronic tuberculosis, or in pneumonia of the asthenic type, or in diphtheria when death results from asphyxia or from paralysis of the diaphragm, considerable amounts of lipoids are still present in the cortex. The load of adrenalin is diminished to a varying extent in these conditions, but not to the same extent as the load of lipoid in the cortex. Nor is there any parallelism between the two. Goldzieher, whose observations are based on 4000 autopsies, also found a considerable reduction in the load of adrenalin. He gives an average of 1·5 mg. of adrenalin in septic infections as compared with 4 mg. in the gland of the normal adult.

Another indication of a selective participation of the gland in bacterial infections is the greatly increased hyperæmia of the gland. Goldzieher refers to the frequent occurrence of such pathological changes in the adrenals

in septic infections as congestion with, or without, hæmorrhages, thrombosis, necrosis, etc. He states, in fact, that such changes are not the exception, but are a constant occurrence in septic infections, and contrasts this frequency with the rarity of such changes in other organs. According to Symmers (1919) intense congestion of the suprarenals is a common post-mortem lesion in influenza, and may be sometimes associated with hæmorrhagic extravasation into the gland. The evidence of other authors concerning the occurrence of adrenal hæmorrhages in the course of acute bacterial infection resulting from the intense congestion of the gland in these conditions has already been discussed (see p. 114).

The evidence of human pathology confirms, therefore, the results of experimental observation in showing that many bacterial infections produce profound changes in the adrenal glands. The results of our experimental observations enable us to interpret these changes. The intense hyperæmia indicates an increased secretory activity of the gland. The diminution in the load of adrenalin does not in itself necessarily mean an exhaustion of the gland as many writers have supposed. The load of adrenalin represents the balance between the rate at which adrenalin is formed and the rate at which it is secreted. A gland may therefore continue to secrete adrenalin actively, though its load is greatly reduced, provided that the new formation of adrenalin is not impaired. We have given reasons for our view that this —the rapid new formation of adrenalin—is dependent upon the functional integrity of the cortex. We do not yet know whether the cortical lipoid is directly concerned in this process, or whether its presence in the resting gland and the changes in its distribution when the adrenal gland is stimulated to activity are merely a visible expression of the functional state of the cortical cells. Since we have seen that the cortical lipoid disappears when we impose an inhibition upon adrenal activity by exposing an animal

to a hot environment for long periods, we may look upon this disappearance of the cortical lipoid as indicating a functional inhibition of the cortex. The disappearance of the cortical lipoid as a specific result of bacterial infections of such virulence that they lead rapidly to a fatal issue is capable of the same interpretation. But it must be understood that this inhibition of the cortical activity is attributed, not to bacterial infections as such, but only to bacterial infection of outstanding virulence.

T. R. Elliott (1914) has stated that " the load of lipoid is not directly related to that of adrenalin ". Our observations agree with this statement in the sense that a medulla may be depleted of adrenalin, while the cortex may be either filled with lipoid or empty of it. But there is this important functional relationship—that so long as the cortex is full of lipoid a depleted medulla may refill itself rapidly with adrenalin, and may in fact be still secreting adrenalin as fast as it can form it. In the absence of lipoid the new formation of adrenalin is impaired, and the condition of such a gland may be described as being in a state of exhaustion. It is in agreement with this view that removal of the adrenal glands renders an animal more susceptible to the lethal action of bacterial intoxications as shown, for instance, in the experiments of Scott (1924) and of Gottesman (1926).

Thyroid Gland in Bacterial Infections.

The thyroid gland also shows changes in bacterial infections. Roger and Garnier (1898, 1899) appear to have been the first to point this out, and their observations have been confirmed by a number of authors (Toni, 1900 ; Kashiwamura, 1901) ; especially by de Quervain (1906) and his collaborators (Sarband, 1906). More recently Farrant (1914) and McCarrison (1917) have again emphasised the effect of bacterial toxins on the thyroid gland. The toxins of intestinal worms (*Ascaris*, *Tænia*)

also produce an effect on the thyroid as they do on the adrenal glands (Bedson, 1913).

The changes which have been observed in these pathological conditions are hyperæmia, desquamation of epithelium and disappearance of colloid. There is reported also a diminution in the iodine content of the gland (Aschenbacher, 1906). Recently Fellenberg (1923) has observed an increased iodine excretion in fever. We may add to this from a study of our own pathological material that occasionally small hæmorrhages occur into the alveoli, so that the "ghosts" of red corpuscles can occasionally be seen lying in the colloid. There has been some discussion about the interpretation which is to be placed upon these histological changes. Our experimental observations show that they indicate a hyperactivity of the thyroid gland—a view which confirms Roger and Garnier. A comparison of Plate 34, which represents a human thyroid from a case of meningitis with a prolonged severe pyrexia, with Plate 33, from a rat after the injection of T.H.N., shows an almost identical appearance. There are also very definite and distinct changes in the mitochondria and the Golgi apparatus in the cells of the thyroid gland in different stages of activity (Cramer and Ludford, 1926). But since these cytological changes can be detected only in tissues fixed immediately after death, these criteria cannot be applied to human post-mortem material.

Not all bacterial infections possess this stimulating action on the thyroid to the same degree. According to some authors, scarlet fever, typhoid fever and tuberculosis in their acute forms have a particularly "thyrotonic" effect. Plate 35 is a drawing of the thyroid gland of a boy, aged four, who died from miliary tuberculosis. For the last two months he had shown a hectic temperature and he died in hyperpyrexia (104·5° F.). The gland was deeply congested. The greater part of the section consists of alveoli free from colloid and lined by pro-

liferating epithelium, giving a picture similar to that seen sometimes in exophthalmic goitre. In some parts of the section the epithelial proliferation together with the congestion produced an appearance which made it difficult to identify the tissue as being thyroid gland. The field drawn has been selected so as to show a few alveoli of normal size and appearance in contact with others exhibiting loss of colloid and epithelial proliferation. McCarrison holds that the toxins of these organisms whose normal habitat is the intestinal canal, such as *B. coli*, dysentery bacilli and cholera bacilli, exercise a particularly profound effect on the thyroid. An interesting observation of comparative pathology bearing on the participation of the thyroid gland in the fever accompanying bacterial infections has been recorded by J. A. Murray (1918). On the basis of a systematic examination of the thyroid gland of warm- and cold-blooded animals which had died in the Zoological Gardens as the result of severe infections he reports as follows : " In warm-blooded animals dying under these conditions extreme congestion of the whole gland is practically constant. Nothing of the kind has been encountered in the reptiles examined, although a large proportion presented severe septicæmic conditions after death. The result is unfavourable to the view that the thyroid plays the part of a neutraliser of toxic substances in the body. It is in much better harmony with the view that the changes in the thyroid in these conditions are the expression of its participation in the heat-regulating mechanism of the body. In poikilothermic animals one would expect these changes to be absent."

In warm-blooded animals the effect of bacterial infections may lead to a functional exhaustion of the thyroid or there may be organic changes, such as sclerosis, which Roger and Garnier observed after tubercular infection. It is well known that acute infections are sometimes followed by symptoms which may not unreasonably be

attributed to disturbances of the thyroid or adrenal function. The stimulation produced by the toxins may develop into Graves' disease. Such cases have been reported as following upon influenza, typhoid fever and articular rheumatism (Falta, 1913). Or the function of the gland may be impaired as the result of exhaustion. Obesity after recovery from typhoid or from tubercular infection, the falling out of hair and the general asthenia and mental depression after influenza are examples. Even myxœdema and Addison's disease have been known to develop after acute infections. Fulchiero (1923) has reported three cases of malaria having all the classical symptoms of Addison's disease. Sergent and Oury (1923) describe a case of adrenal insufficiency following upon typhoid fever. Reference may be made here again to the fact that many bacterial toxæmias and bacterial infections in cases of diabetes mellitus aggravate the hyperglycæmia and glycosuria and render such cases more resistant to treatment by insulin. It has been pointed out in the chapter on the glycogenic function of the liver that this effect finds an explanation in the increased activity of the thyroid-adrenal apparatus and the resulting stimulation of the glycogenic function of the liver, so that more glucose is passed into the blood (see p. 88).

Human and experimental pathology furnish evidence, therefore, that in many bacterial infections the thyroid and adrenal glands are strongly affected, particularly in the acute types of infections, such as malaria and influenza, which are accompanied by the greatest disturbances of the heat-regulating mechanism.

Therapeutic Applications: Significance of Fever.

This conclusion suggests therapeutic application. In those infections which, like diphtheria, have a particularly adrenalotoxic effect, and in which the temperature is normal or subnormal, it should be of special importance

to keep the patient warm so as to relieve the adrenal from the strain of heat regulation. In the case of gas gangrene it could be shown experimentally (Bullock (Gye) and Cramer, 1919), that exposure to cold could transform a non-lethal dose into a lethal dose. The injection of adrenalin ought to be of special value in acute bacterial infections where there is a sudden failure of the circulation. This is usually ascribed to heart failure, frequently without any pathological evidence. It may be due to the exhaustion of the suprarenals. In a paper published seventeen years ago, John (1909) claimed to have obtained excellent results by the intravenous injection of adrenalin in diphtheria. It may be equally indicated in other acute infections. And if the post-influenzal depression is an expression of an exhausted thyroid-adrenal apparatus, it ought to be possible to counteract it by the administration of adrenalin or of thyroid gland. The mode of action of these substances suggests the use of adrenalin in acute conditions, especially in acute failure of the circulation, while thyroid administration is indicated in convalescence after a severe infection, such as influenza for instance. In the only two cases in which I have been able to test the effect of thyroid administration to relieve post-influenzal depression the result fulfilled the expectation. Clemente (1920) records two cases of post-influenzal asthenia in which rapid improvement followed administration of suprarenal extract. The manic-depressive psychosis following influenza has also been attributed to adrenal insufficiency : the same treatment appears indicated.

It is fairly generally agreed to look upon the fever accompanying bacterial infections as a defensive reaction of the organism, in which the rise in temperature is the essential factor. We see now that in many of these fevers there is, in addition to the rise in temperature, yet another factor which may be operative, namely, the pouring into the blood of the thyroid and adrenal hormones and the

resultant general sympathetic stimulation. Further investigations will have to show whether these latter factors represent an essential part of the mechanism of defence against bacterial infection, and whether the fever is perhaps a less essential feature than has been believed. It is suggestive that conditions such as excessive exposure to cold and anæsthesia, which tend to exhaust the thyroid-adrenal apparatus, are frequently followed by infections of the respiratory tract and that the same infections are stated to supervene frequently in untreated cases of myxœdema. On this argument the greater susceptibility of cooled animals to infection appears as the result of the exhaustion of the thyroid-adrenal apparatus, and is not, as is at present supposed, the direct result of the lowering of the body temperature.

The fact that many bacterial toxins stimulate the thyroid-adrenal apparatus illustrates perhaps the curious and as yet unexplained phenomenon that in some infections the injection of non-specific vaccines and even of proteins may sometimes have a striking therapeutic effect. The effect of the injection of these substances is to produce a typical rigor. The rationale of this so-called non-specific vaccine therapy and protein therapy would be that it elicits an increased functional activity from the thyroid-adrenal apparatus—in fact sympathetic fever, which is one of the normal reactions of the organism against bacterial infection.

The intense sympathetic stimulation which is present in the type of bacterial infection accompanied by a rigor might also explain two characteristic effects: the characteristic constipation could be explained by the inhibition of intestinal movements from sympathetic stimulation; the pulmonary œdema and congestion would also necessarily follow as a result of prolonged sympathetic stimulation. We can readily understand how in such a virulent general infection as influenza the lungs, becoming congested, offer a ready soil for a localised

infection, so that a pneumonia develops. It has long been a puzzling feature of influenza epidemics that the disease tends to be more fatal to vigorous individuals. In these the adrenals react most strongly to the stimulating action of the influenza toxin, just as experimentally well-fed and strong animals react most powerfully to the stimulating action of β-tetrahydronaphthylamine.

Summary.

In the preceding pages evidence has been adduced to show that the thyroid and adrenal glands form a humoral apparatus concerned in the heat regulation of the body. For the purpose of this chapter the conception may be summarised by stating that increased activity of this apparatus increases heat production and diminishes heat loss, so that fever is produced.

In this chapter it is shown that an aseptic fever of this kind is also the result of certain pathological conditions involving hyperactivity of these two glands. Examples are Graves' disease and adrenal hæmorrhage. Clinically these conditions closely resemble bacterial infections, and are frequently mistaken for such. Adrenal hæmorrhage in particular is hardly, if ever, diagnosed during life, and usually mistaken for an acute bacterial infection. It is probable that many of the so-called pyrexias of unknown origin are due to disturbances of these two glands.

The similarity between these aseptic fevers and those produced by many microbic infections finds its explanation in the fact that they have the same physiological basis : the adrenal glands and, to a less extent, the thyroid gland are particularly susceptible to the action of many bacterial toxins. Some, for instance diphtheria toxin and the toxins of gas gangrene, have a predominantly toxic action and rapidly exhaust these glands—" adrenalotoxic " and " thyrotoxic " effects. Others have a stimulating action —" adrenalotonic " and " thyrotonic " effects, although

in excessive doses they may also exhaust the glands through over-stimulation. Adrenalotonic and thyrotonic actions are accompanied by fever, adrenalotoxic and thyrotoxic actions by a subnormal temperature. The adrenalotoxic effect plays an important part in determining the lethal issue of many microbic infections. It is pointed out that in so far as fever is a defensive reaction against infections, the essential mechanism of defence may be the secretion of the thyroid and adrenal hormones and the resultant general sympathetic stimulation induced by the action of microbic toxins rather than the rise in temperature by itself.

The conception of the thyroid-adrenal apparatus as a mechanism concerned in controlling body temperature renders it possible to correlate a number of pathological and clinical observations, the significance of which has hitherto been obscure: the endocrine origin of pyrexias of certain diseases of the thyroid and adrenal glands and of acute infections, the symptomatology of adrenal hæmorrhage and its prevalence in infants, and the part played by bacterial infections in determining the onset of diseases of the thyroid and adrenal glands.

Some therapeutic applications of this conception are discussed, and it is suggested that it affords an explanation for the non-specific vaccine and protein therapy.

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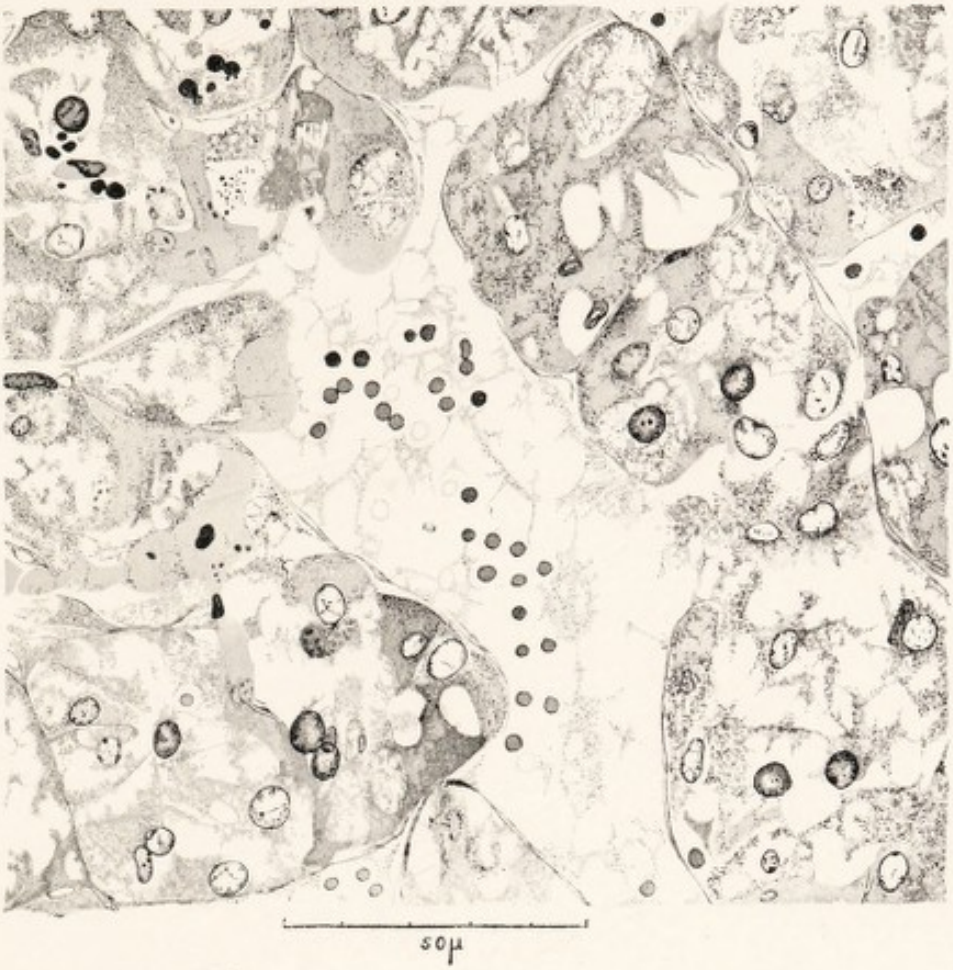

PLATE 32.

High-power view of adrenal medulla of mouse which died twenty hours after injection of 0·5 c.c. of toxin of B. welchii (M.L.D. 0·3 c.c.). Examined one hour after death. The figure shows extreme vacuolisation of medullary cells. Almost all the cells have lost their adrenalin granules, but a few cells with sparse granules can still be seen. There are practically no adrenalin granules in the central vein. The figure illustrates the adrenalotoxic action of certain bacterial toxins. $\times \frac{560}{1}$.

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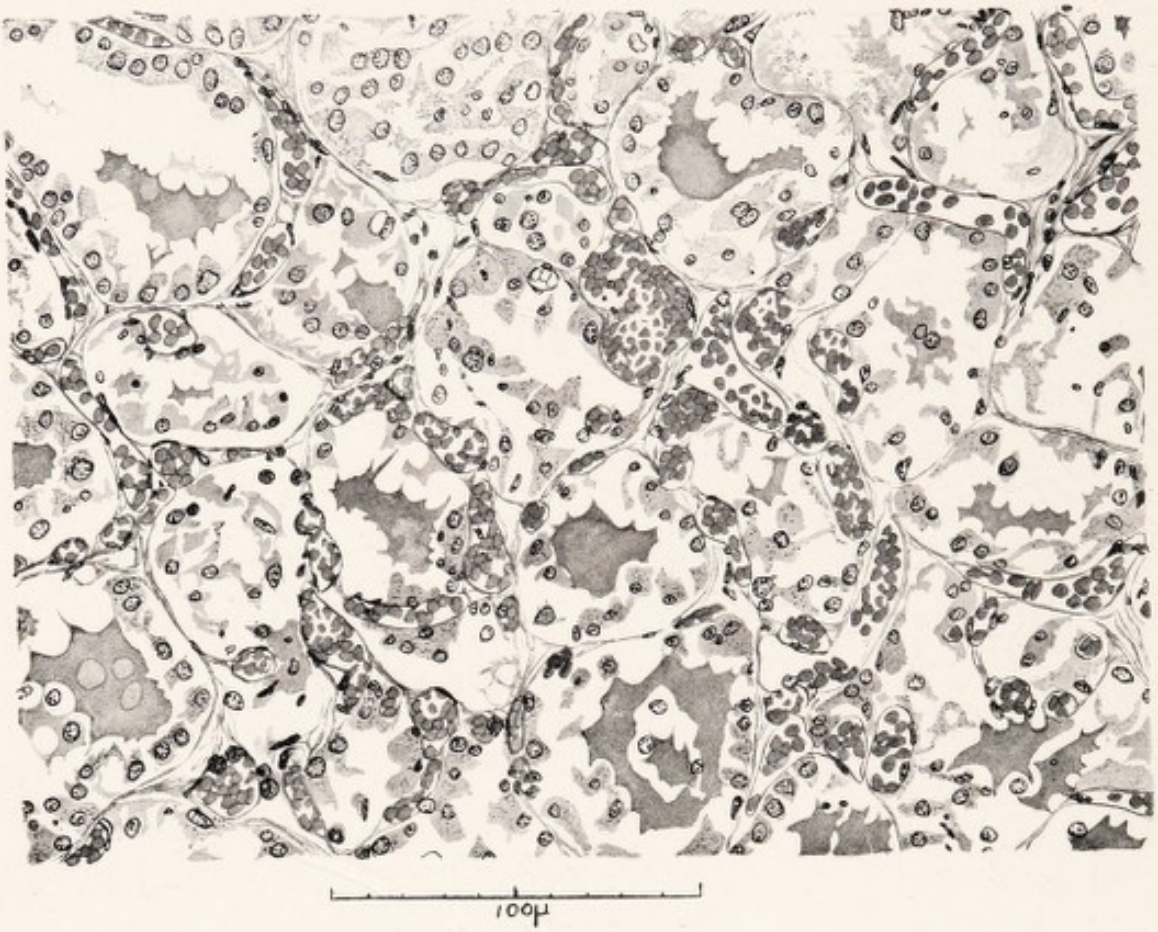

PLATE 33.

Thyroid gland of a rat which died with pulmonary hæmorrhage two hours after injection of 20 mg. of T.H.N. The drawing illustrates the intense vascular engorgement of both inter-alveolar and intra-alveolar capillaries, desquamation of alveolar epithelium and partial disappearance of colloid. Zenker fixation $\times \frac{250}{1}$.

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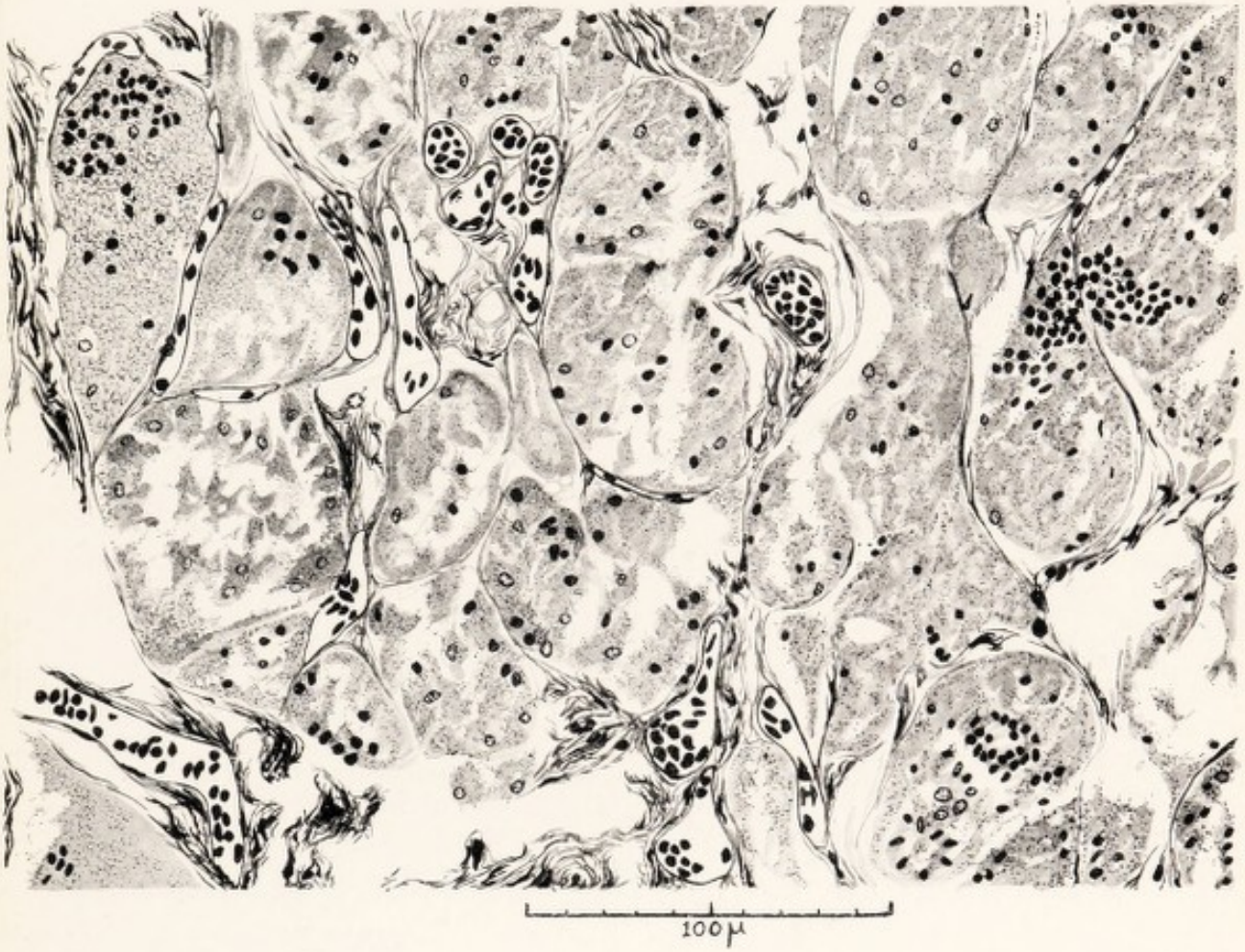

PLATE 34.

Human thyroid gland. Death from meningitis after prolonged severe pyrexia. The figure shows congestion and hæmorrhages into the alveoli, desquamation of epithelium and complete disappearance of colloid. Red blood corpuscles are represented in black. Schridde fixation $\times \frac{360}{1}$.

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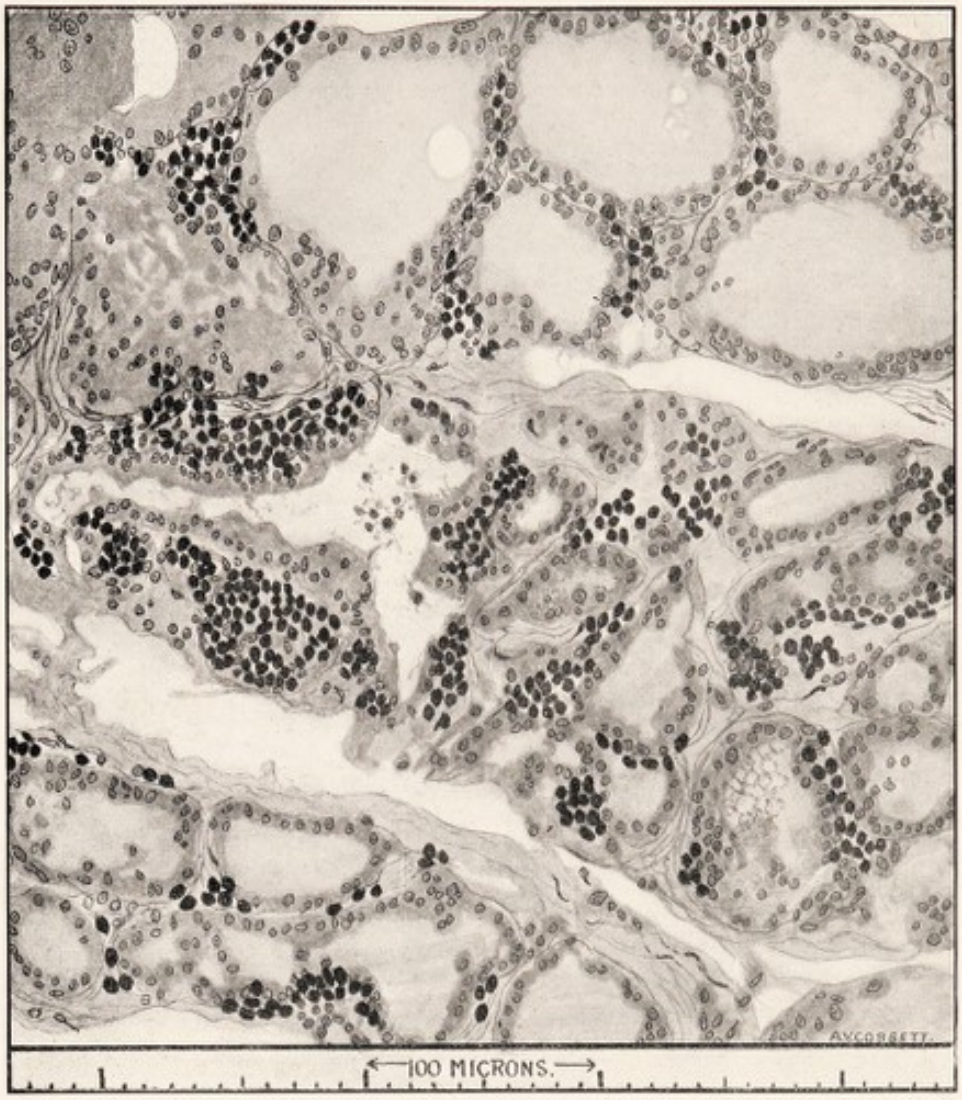

PLATE 35.

Human thyroid gland. Death from miliary tuberculosis in hyperpyrexia (104·5° C.) after prolonged pyrexia. The figure shows intense congestion, and in many alveoli epithelial proliferation and loss of colloid. Although the field has been selected so as to show alveoli exhibiting this change together with alveoli fairly normal as regards appearances of epithelium and presence of a watery colloid, the latter were absent in large parts of the section.

(Reprinted from the *Brit. Journ. of Experimental Pathology.*)

CHAPTER IX

THE THYROID-ADRENAL APPARATUS IN MAN. CLIMATE AND CIVILISATION

THE most fascinating problem of the human adrenal is presented by the changes which it undergoes after birth. The adrenals of the human adult between the ages of twenty and forty years are relatively large organs, their average dimensions being given by Goldzieher as 49 × 33 × 9 mm. for the right gland and 50 × 32 × 9 mm. for the left gland. Their outlines are very irregular and very different in the two glands. This can be seen most clearly from the accompanying photographs which represent sections taken at regular intervals through the right and left adrenal gland respectively (Plate 36). The glands from two different cases are represented. Both were men between fifty and sixty years of age. In one case death was due to an accident, so that the glands in this case are most likely to present the normal appearance of the human medulla. It will be seen that the right and left gland differ so completely in their arrangement that it is possible to identify whether a section belongs to the right or left adrenal. The figure also shows that the bulk of the medullary cells are collected at one part of the gland in each case and occupy there a relatively small space, so that the total bulk of the medulla in the human adrenal is very small. With the help of the photographs it is possible to identify that part of the human gland in which the bulk of the medulla is situated, which may be a convenience to morbid histologists.

Microscopic examination of the human gland shows that the cortex at its inner central end is limited by a relatively strong band of connective tissue. This not only separates the cortex from the medulla, but where there is no medulla it separates the two sides of the cortex from each other. In the presence of this well-developed band of connective tissue the human medulla differs from that of other mammals.

This band of connective tissue does not exist at birth. It owes its origin to an extraordinary change in the gland which sets in after birth and for which no analogy has so far been found among other mammals. The adrenals of all mammals which have been investigated so far present at birth the complete appearance of the fully developed adult adrenal. Not so the human adrenal. It is at birth a large organ with a smooth regular surface. The medulla is small and contains according to Elliott practically no adrenalin at birth. Lucas Keene and Hewer, however, state that the embryonic gland from the eighteenth week onward contains considerable amounts, but not before that date. The periphery is made up of the typical cortex, which surrounds a large " central body " consisting of cells bigger than the cortex, containing granules of fatty material and separated from each other by blood spaces. The appearance is given in Plates 37 and 38, the latter being a higher-power view. When fixed in bichromate solutions the " central body " stains a mahogany brown simulating the chromaffin reaction to the naked eye. But microscopic examination shows that this reaction is given by the blood spaces, not by the cells. This " central body " of cells completely disappears during the first weeks of life as the result of an extraordinary process (Plates 39 and 40). The blood spaces become widely dilated and distended with blood. Then a connective tissue reaction sets in suggesting the organisation of a hæmorrhage. This reaction which begins in the peripheral part of the " central body " cuts off the central

mass from the cortex. At places the large cells of the " central body " can be seen encircled singly or in groups by the connective tissue fibres, and eventually they become strangled by them. At that stage groups of medullary cells appear in the more central parts of the " central body "—those where the medulla is seen in the adult gland—and replace the large cells of the " central body ", while in other parts the connective tissue reaction destroys almost completely the original " central body ". A few of the large cells escape destruction and can be seen even in the adult gland. The band of connective tissue in the human adrenal may be said, therefore, to represent a scar tissue. In the greater part of the gland this scar tissue replaces more or less completely the original " central body ", while at one pole in each gland the true medulla forms within this scar tissue. This reaction, which is responsible for the irregular surface of the fully developed gland, is accompanied by a loss in weight of the gland, so that during the first few weeks of life the human adrenal loses in weight. What is the nature of the " central body " of cells ? The disappearance of the " central body " and its substitution by medullary cells was first described by Elliott and Armour and has been confirmed, amongst others, by Lucas Keene and Hewer. All these authors seem to take it for granted that the " central body " has the same origin as the cortex. They hold that the medulla develops at the expense of the " central body ". My own observations are in agreement with those just mentioned, so far as the main facts concerning the process are concerned. In some of my preparations, however, I have observed appearances which suggest that the large cells of the " central body " are not replaced by medullary cells, but themselves form the medullary cells by breaking up into the smaller cells which represent the medulla of the adrenal gland. If that interpretation is correct we would have to look upon the " central body " as the origin of, at any rate, part of the medulla. The solution

of the problem obviously depends on embryological data, which are at present not yet available, as to whether the cells of the " central body " are derived from sympathetic ganglion cells or whether they have the same origin as the true cortex. The mere fact that the cells of the " central body " contain fatty globules is not evidence that they are cortical in origin. We have seen how in the mouse adrenal cells, which undoubtedly belong to the medulla, completely lose their typical appearance when they lose their load of adrenalin and assume the appearance of cortical cells. The cells of the " central body " certainly differ from the true cortex in being very much larger, as the figures show, and Lucas Keene and Hewer suggest that they have a different origin. It is interesting to note that Marine and his collaborators found a definite rise in heat production beginning in the second week of life, which, as they suggest, may be related to this process of involution.

A process of this kind offers ample opportunities for abnormalities to occur. We have noted in a cretin that this formation of the medulla is inhibited, although the connective tissue reaction has commenced. The absence of a " central body " (fœtal cortex) in anencephalous monsters has been reported by the authors quoted above. As Elliott and Armour put it, " the suprarenal of a brainless child develops in the same manner as that of animals ". In the adrenal of infants dying in the first three months of birth with the symptoms of marasmus an imperfect development of the medulla was found. The material at our disposal was not sufficiently large to enable us to draw definite conclusions. It is sufficient to suggest, however, that the pathology of the human adrenal during the first few months of life offers a wide field of study which is likely to yield interesting results.

We have already referred (see Chapter VIII.) to the importance which must necessarily attach to the sudden change in the thermal environment occurring at birth.

This change is probably responsible for initiating this process by inducing the intense hyperæmia which elicits the connective tissue reaction. If the suggestion is correct it seems possible that the process may take an abnormal course if the stimulation by the thermal environment is either excessive or inadequate, that is to say, if the infant is kept either too cold or too warm. There is also the possibility that dietetic errors may be responsible for abnormalities in this process. Several observers (McCarrison, Kellaway, Swale Vincent) have shown that both vitamin B deficiency and chronic starvation produce changes in the adrenal gland of animals. Our own unpublished observations on the mouse adrenal have also demonstrated definite changes similar to those described in Chapter VII. on Inhibition and Self-Control of the Adrenal, namely a loss of lipoid in the cortex and an impaired formation of adrenalin by the peripheral cells of the medulla. It is not unreasonable to suppose that such factors, if they are operative during the first weeks of life of an infant, would interfere with the normal course of the process described above which is peculiar to the human race.

An excessive connective tissue reaction or an imperfect transformation of the cells destined to form the medulla may be the cause of some of the obscure diseases of infancy which are classed together under the term marasmus and which are not obviously due to dietetic errors. If that were so the administration of thyroid gland in very small doses or of a few drops of adrenalin suggest themselves as therapeutic measures. Dr. D. Patterson of the Sick Children's Hospital, Great Ormond Street, has tested this suggestion. He found that in a few cases of a certain type of marasmus, which did not yield to dietetic treatment, the addition of three to five drops of adrenalin solution 1 : 1000 to every bottle of milk rapidly improved the condition.

The process which takes place at birth in the human adrenal is at present an unsolved problem. It would be

interesting to know whether a similar process occurs in the anthropoid apes. So far as is known at present it is without analogy in all the other mammals in which the development of the adrenal has been studied. But man differs from all other mammals in the fact that his heat-regulating mechanism is so imperfectly developed that he can only maintain his body temperature by the aid of clothing and artificial heat, except in tropical climates. In fact, Rubner has shown that the effect of clothing is to create a thermal environment for his skin which practically corresponds to that of a tropical climate. Civilised man behaves, so far as his heat regulation is concerned, like an animal kept at an outside temperature of 33° C. Under such conditions the chemical heat regulation is practically eliminated and only the physical heat regulation remains effective, which controls the heat loss. For this work the activity of the sweat glands is of such outstanding importance that their failure to work in a warm environment induces heatstroke. Hearn has pointed out that every attack of heatstroke is ushered in by a failure to sweat, and this prodromal sign occurs many hours before the rise of temperature sets in, so that it is possible to avert successfully every case of heatstroke by instituting treatment with wet blankets whenever failure to sweat makes its appearance.

But there are animals that do not possess sweat glands except in certain restricted sites, such as the pads of the feet, and that cannot therefore increase their heat loss by perspiration. To this group belong most of the animals with a thick fur—practically all the animals used for experimental purposes—rat, mouse, rabbit, guinea-pig, cat and dog. This represents a difference of greater significance than is generally recognised. For while man —and with him those animals possessing a wide distribution of sweat glands (for instance the horse and the pig)— is capable of withstanding temperatures greatly exceeding those of his body, animals without sweat glands are

not able to do so. We have found that under experimental conditions in a still atmosphere mice and rats die as soon as the outside temperature rises above 38° C., and the post-mortem examination shows exactly the same lesion that is described as most characteristic of heat-stroke in man: deep engorgement of the lungs. Conversely, man without the aid of clothing would be unable to live in any but a hot or tropical climate, partly because his hairless skin gives him little assistance in preventing heat loss and partly because his chemical heat regulation is less effective. The origin of man, therefore, could only have taken place in a tropical climate. The importance of the endocrine organs for the process of evolution and for the differentiation of mankind into racial types has been repeatedly emphasised, most convincingly perhaps by Sir Arthur Keith. Since changes in the thermal environment affect so profoundly at least two of these organs it follows that climate is a factor of considerable evolutionary importance.

Man by the invention of clothing and of fire has made himself within limits master of his climatic environment. Man can live in practically all the climatic conditions existing on earth. But climate affects him in many subtle ways, not only physically but also mentally, to a much greater degree than is generally suspected. Ellsworth Huntington has collected a wealth of interesting material bearing on this point in a book entitled *Civilisation and Climate*, from which the following data are quoted as examples. He has studied the effects of changes in the weather on a great many different forms of human activity, both mental and physical. In this way he has been able to establish definite variations. Both physical and mental activity reach pronounced maxima in the spring and in the autumn with minima in midsummer and midwinter. Further analysis shows that the most important climatic factors are, in the order of decreasing importance, (1) the mean temperature month by month;

(2) the amount of change in the weather from one day to another ; and (3) the relative humidity. There are other minor factors, but one interesting and unexpected conclusion is that changes of temperature, provided they are not too great, are more stimulating than uniformity. In the temperate climates a fall is more stimulating than a rise, and people are not so efficient on fine days with a clear sky as on cloudy days or after a storm. The greatest efficiency in physical and mental activity is found with a mean temperature lying between 50° and 60° F. ; it falls rapidly as the mean temperature rises above 65° F. It thus becomes possible to establish what constitutes an " ideal " climate—ideal from the point of view of human efficiency. Meteorological data show that climatic conditions approaching this ideal cover the greater part of Western Europe, stretching as far as the eastern borders of the Baltic, the southern parts of France and the northern part of Italy. It is satisfactory to find that the climate of England comes nearest the ideal. The climate of Japan, New Zealand and the south-eastern corner of Australia also approaches the ideal. On the American Continent we find such a climate in a broad belt running parallel with the Canadian border and comprising southern Canada and the eastern and central states and also in a narrow stretch on the Pacific Coast from British Columbia to California. The localities mentioned above are exactly those where human activities have reached their highest development. They are the centres of our present civilisation. It will be noticed that a climate which has been found to be ideal from the point of view of human efficiency is not one which is most pleasant or most comfortable. Comfort does not make for human progress.

Climate is not constant. There is evidence that there have been climatic alterations in historic times, and Huntington makes the bold suggestion that these " climatic pulsations ", as he calls them, are responsible for

the shifting of the centres of civilisation which have occurred. Here Huntington has perhaps not taken into consideration sufficiently that the factors constituting our "ideal" climate, from the point of view of human efficiency, are dependent partly on the extent to which man by housing, artificial heating and clothing can modify his climatic environment. In the days when Egypt and Greece were the centres of civilisation the climate of Western Europe, even if it were the same as it is now, may not have presented the conditions most favourable to the highest development of human faculties, because then man had not yet succeeded in eliminating the depressing effect of a cold climatic environment to the same extent as he has now.

Climate is of course not the only factor in determining the condition of civilisation, or even the main one. But its influence is such that "no nation has risen to the highest grade of civilisation, except in regions where the climatic stimulus is great".

The effects of climate on our physical and mental well-being are, of course, familiar to everybody. We speak of a "bracing" climate and a "relaxing" climate, and the beneficial effect of climatic variations finds its expression in our desire for a "change of air". Our observations on the thyroid-adrenal apparatus supply the physiological basis for the interesting relationship between climate and civilisation which has been illuminated by the work of Huntington. In this connection it is interesting to recall that a change from a warm to a cool environment was found to be a much more powerful stimulus to the adrenal gland than a continuously cool environment. This may be the manifestation of a general biological law which applies to all reactions of living cells to their environment, namely that these reactions depend upon a change in the conditions of the environment rather than upon the environmental condition itself. The fact that the activity of the thyroid and adrenal

glands are subject to climatic conditions enables us to understand the effects of climate on man. For, in man at any rate, these glands are not merely regulators of metabolism, of heat production and heat loss. Their functional state affects his physical activities and colours his mentality. We need only think of the physical lassitude in Addison's disease, the degradation of intelligence which accompanies even the earliest onset of myxœdema, and the restoration to normal mentality through administration of thyroid gland. In connection with the remarkable effect of thyroid medication we may recall the statement of Gley: " Le genèse et l'exercice des plus hautes facultés de l'homme sont conditionnés par l'action purement unique d'un produit de secrétion. Que les psychologues méditent ces faits ! "

These pathological conditions form a counterpart to the depressing effect of a warm, moist climate with little change from day to day. We feel it to be " relaxing ", because it fails to stimulate the thyroid-adrenal apparatus and through it the sympathetic. Conversely the cool, variable climate which we have learned to associate with the fullest development of human activities provides a continued stimulus to these endocrine organs and the sympathetic.

The same explanation applies to the relations between climate and health. Why is the resistance against certain bacterial infections, such as tuberculosis, increased by a suitable cool, dry climate, and by measures such as open-air treatment, hydrotherapy and the like ? Hitherto we have been told that these conditions increase metabolism. But though the metabolism is increased by such measures that in itself does not explain the beneficial effect. An increase in metabolism can be induced by other measures, such as vigorous muscular exercise, but then it is likely to be harmful. The answer to the question is that those measures are beneficial that stimulate the thyroid-adrenal apparatus without exhausting it, and thus strengthen

what we have seen is one of the normal reactions of defence of the organism against many bacterial infections. The increased metabolism is merely the outward manifestation of this stimulation.

Conversely a warm, moist, monotonous climate weakens resistance against infections, not because it reduces metabolism, but on account of the continued absence of a stimulus to the thyroid-adrenal apparatus and the sympathetic. An interesting example of this relationship has come to light recently as the result of the work of a Committee on the Atmosphere and Man appointed by the National Research Council of the United States, quoted from Huntington, *Civilisation and Climate*. During the influenza epidemic of 1918 the severity of the disease varied greatly from place to place in the United States. On comparing the deaths from influenza and pneumonia with various environmental factors, it was found that the severity of the disease depended upon the weather more than upon any other known factor. The epidemic was most severe in the warm parts of the States and those cities in the cooler parts which happened to be especially warm before and during the epidemic. Where people were weakened by hot damp weather the influenza became virulent, it spread with great rapidity and it entailed a huge death-roll.

The depressing effects of inefficient ventilation, which the work of Leonard Hill has shown to be due to lack of cooling power and not, as was at one time supposed, to an excess of CO_2 in the air or to other toxic substances, are similarly due to this lack of a stimulus to the thyroid-adrenal apparatus. Conversely, we have the intensely depressing effect resulting from exposure to cold, with insufficient clothing and inadequate heating. This leads to a mental and physical deterioration through exhaustion of the thyroid-adrenal apparatus.

At the other extreme is the effect of a tropical climate on man. This has frequently been attributed to a pro-

gressive decrease in the basal metabolism. But actual measurement has shown that the basal metabolism of a European in a tropical climate is not lower than that of the same European in the cooler climate of his native country. Nor is there marked difference between the basal metabolism of a European and of a native who is better able to withstand the climate than the European. There must, therefore, be some factor, in addition to the lack of stimulus, which makes the European less fitted to adapt himself to a tropical climate. The following considerations are offered as a possible solution of this problem.

As long as the thermal environment provides an efficient stimulus the thyroid and adrenal glands are not only actively secreting their specific hormones but are as actively forming it. When this stimulus is absent not only their secretion but also their formation is inhibited. We have seen that in the adrenal this inhibition may go so far that the peripheral parts of the medulla cease to contain adrenalin. What then happens to the precursors of adrenalin and of thyroxin respectively? The possibility must be considered that an abnormal accumulation in the blood-stream of these substances may produce pathological effects. There is a close chemical relationship between adrenalin and pigment. It has been shown that pigment can be formed from adrenalin and substances allied to adrenalin by a special ferment. Pigment granules are often found in the zona reticularis of the adrenal gland, that is to say, in the same region where, in increased activity of the gland, granules of adrenalin or a precursor of adrenalin are found. When owing to disease of the adrenal medulla or in Addison's disease the formation of adrenalin is impaired, pigment is deposited in the skin. The pigmentation of the races living in tropical climates may perhaps be the method by which the organism disposes of the material which would otherwise have been used for the formation of adrenalin. In

the white races this method of excretion of the excess of adrenalin of its precursor is not so well developed and this may be one of the reasons why the white races are less fitted for a tropical climate.

The study of the physiological basis of the effect of climate on man shows us man fashioning his own development by struggling to free himself from his climatic environment. We have seen that man in his natural state is unfitted to exist in any but a tropical climate. But this is the very climate which places a limitation on his mental development. The invention of clothing and, even more, of fire freed him from his thermal environment and enabled him to establish himself in climatic conditions where his mental and physical energy could find their highest development. We may have forgotten what the invention of fire meant to mankind. Primitive man expressed its deep significance in the Promethean myth that fire was a secret stolen from the gods to render man like unto them.

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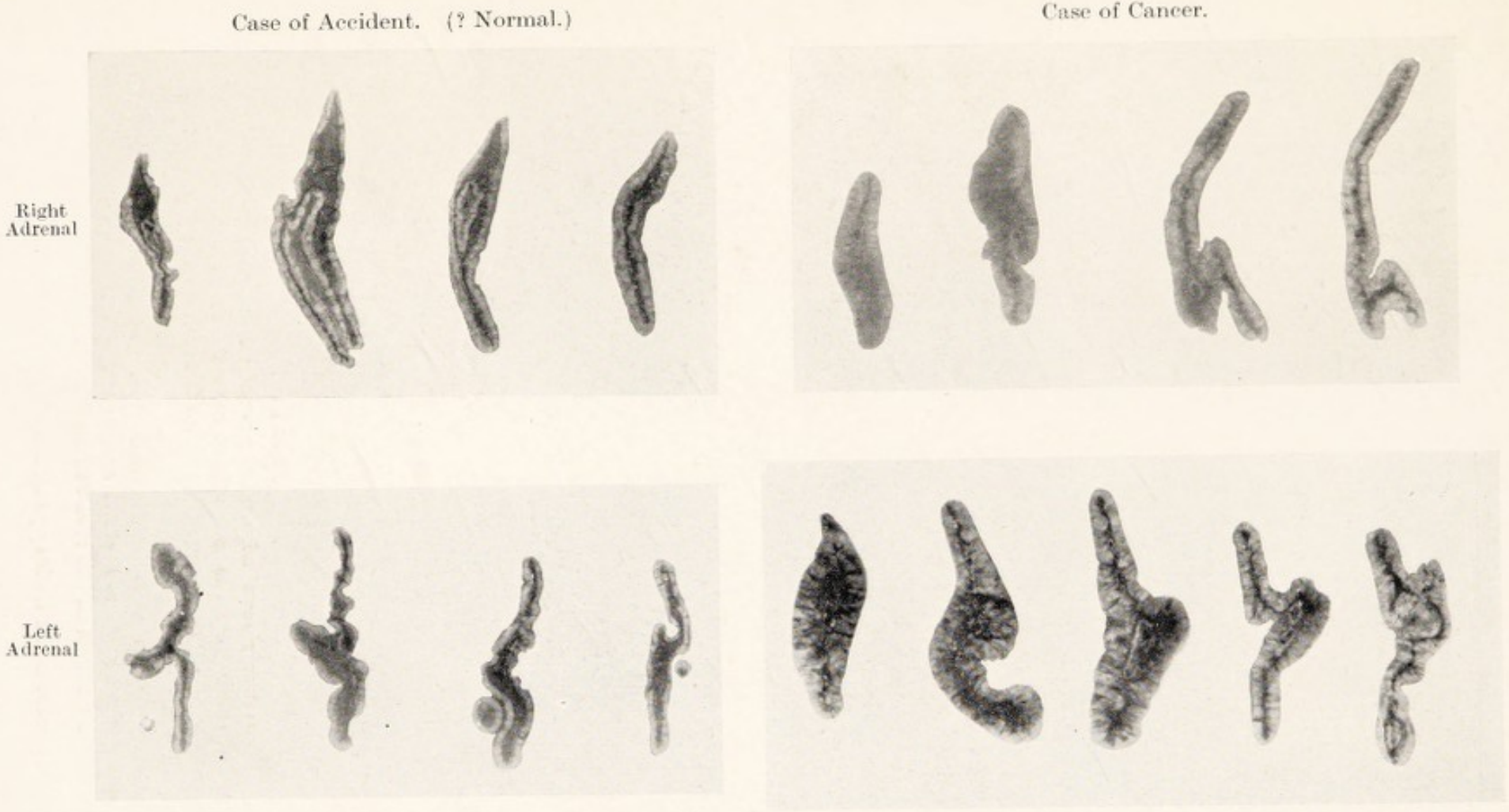

PLATE 36.

Photographs of sections in approximately even intervals of Right and Left Adrenals of two middle-aged men. The glands had been fixed in Formol-bichromate solution. The chromaffin reaction of the medulla was deeper in the accident case than in the case of cancer. The cortex containing lipoids appears lighter. The figure illustrates the great variability in the structure of the human medulla.

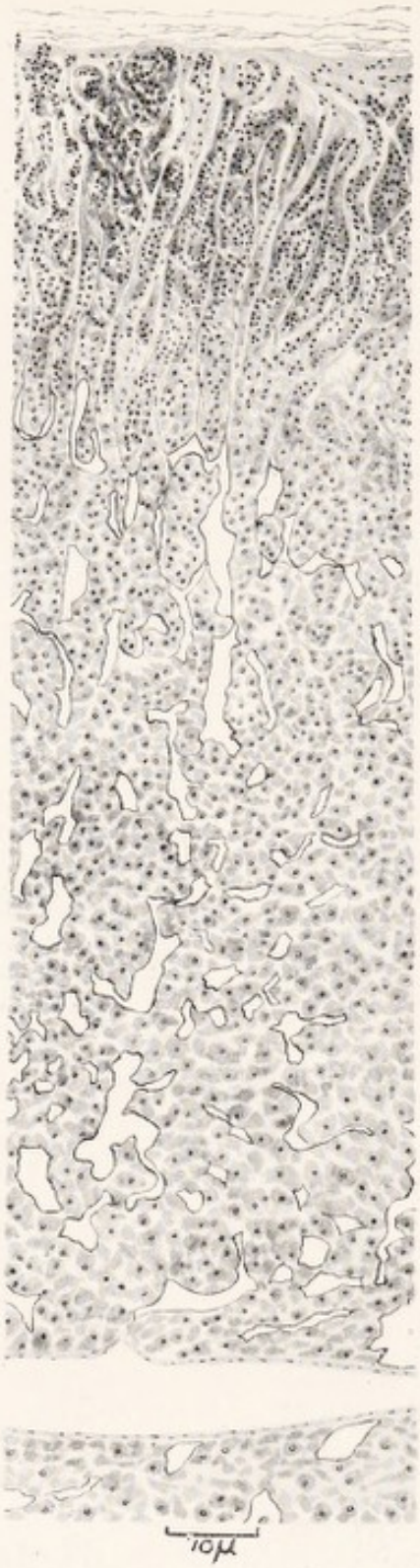

PLATE 37.

Low-power view of adrenal of premature baby. The drawing shows in the upper part the permanent cortex and in the lower part the central vein. The intermediate space is taken by the " central body ", which contains large blood spaces. The latter are left empty in the drawing for the sake of contrast. In the actual preparation they were packed with red blood corpuscles, which were stained a deep mahogany brown as the result of fixation in formol bichromate. These blood spaces make their appearance only in the " central body ". $\times \frac{90}{1}$.

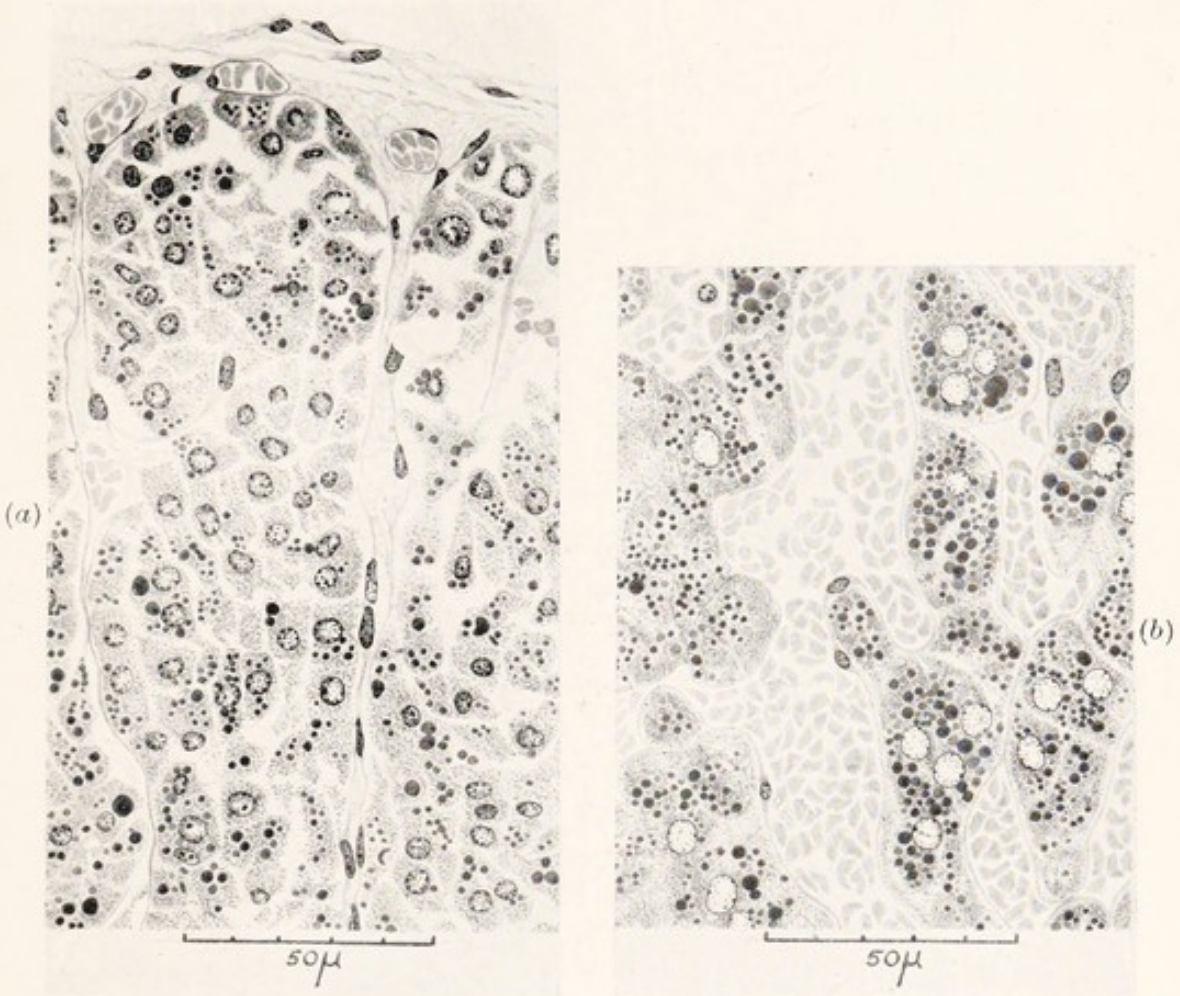

PLATE 38.

High-power view of permanent cortex and "central body" of the same adrenal. 38*a* represents the permanent cortex, composed of small cells arranged in columns containing lipoid globules. The blood vessels are not dilated. 38*b* represents a few cells of the "central body" surrounding a dilated blood space filled with red blood corpuscles. The cells of this central body, which also contains lipoid globules, are very much larger than the cells of the permanent cortex; some are multinucleated. $\times \frac{470}{1}$.

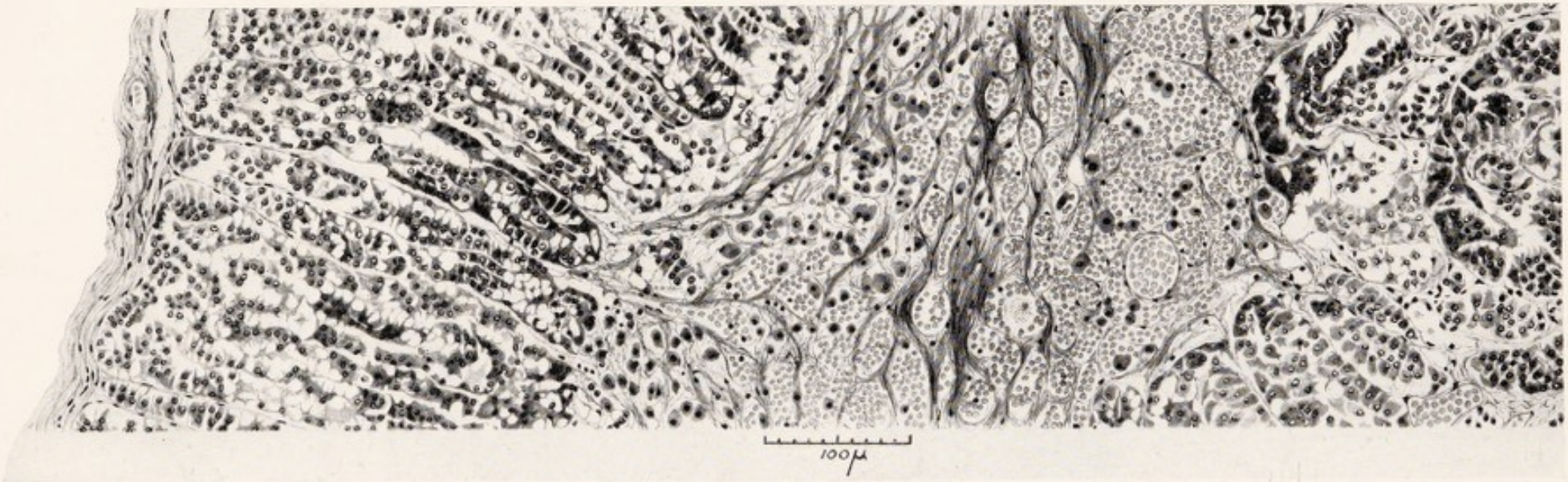

PLATE 39.

Adrenal gland from a child aged five weeks which died in a condition of marasmus. The figure illustrates the disappearance of the "central body" as the result of the process resembling scar formation, described in the text. Note the extreme congestion in the part formerly occupied by the "central body". Many isolated cells of the original "central body" can still be seen, being encircled by strands of connective tissue. This connective tissue reaction separates the permanent cortex from the medulla, which has now been developed. Some of the remaining large cells of the central body are distributed to the cortex as the result of this reaction, others to the medulla.

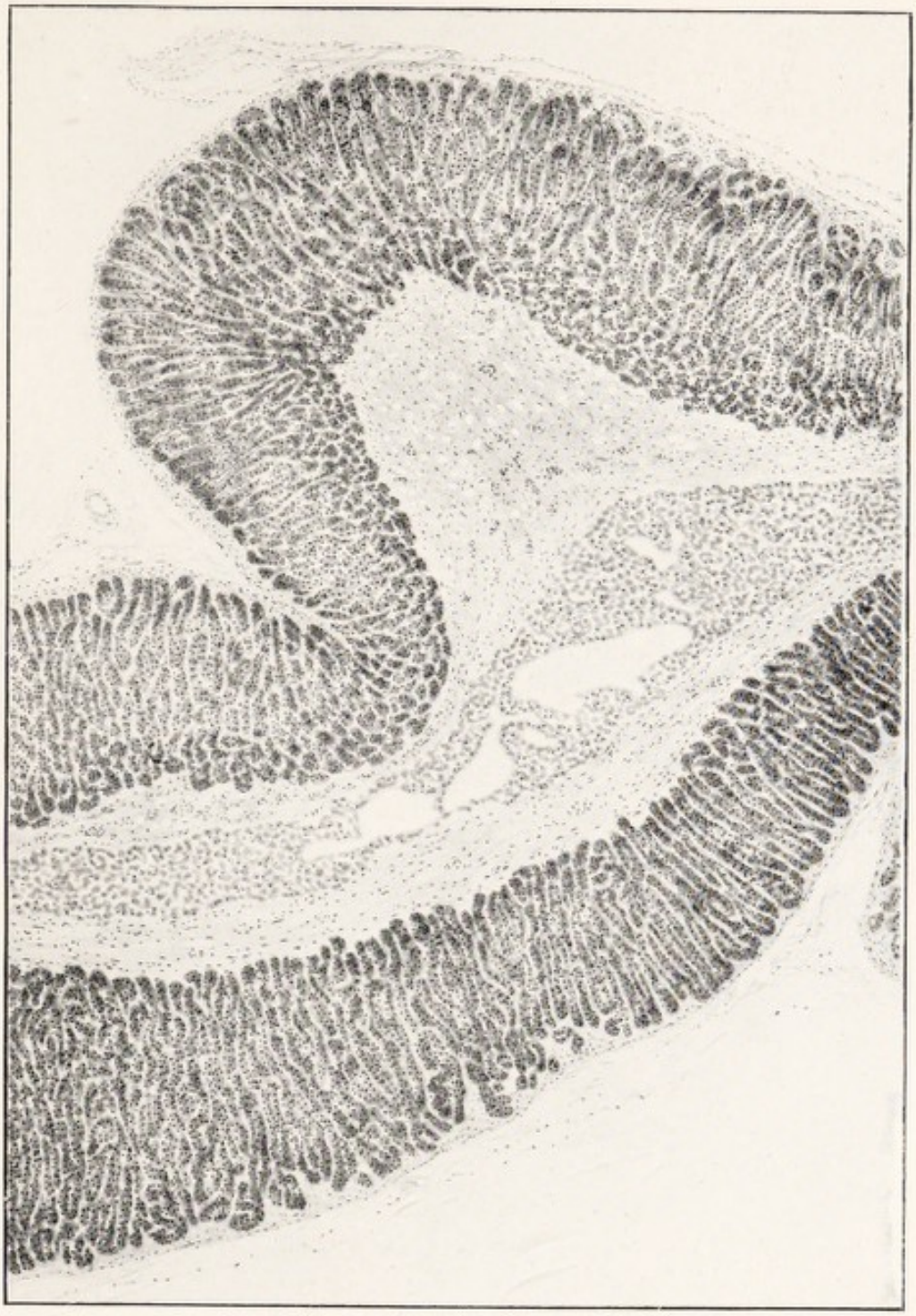

PLATE 40.

Adrenal gland from child aged twelve weeks which died in a condition of marasmus. The section is taken from that part of the gland where the medulla was most fully developed. The scar formation appears to have become excessive, the connective tissue between medulla and cortex being thicker and denser than normal. The chromaffin reaction of the medulla was faint. The cortex was almost free from lipoid.

INDEX

THE END

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