The doctrine of the internal secretory activity of glands in relation to the pathological anatomy of sundry morbid conditions : diabetes, Addison's disease, myxoedema, cretinism, Graves' disease and acromegaly / by J. George Adami.

THE DOCTRINE OF THE

INTERNAL SECRETORY ACTIVITY OF GLANDS,

IN RELATION TO THE

PATHOLOGICAL ANATOMY OF SUNDRY MORBID CONDITIONS.

DIABETES, ADDISON'S DISEASE, MYXOEDEMA, CRETINISM, GRAVES' DISEASE AND ACROMEGALY.

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THE DOCTRINE OF THE INTERNAL SECRETORY ACTIVITY OF GLANDS IN RELATION TO THE PATHOLOGICAL ANATOMY OF SUNDRY MORBID CONDITIONS.[1]

(OF DIABETES, ADDISON'S AND GRAVES' DISEASES, MYXŒDEMA, CRETINISM AND ACROMEGALY.)

BY

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To remove an organ and study the effects of the operation is clearly an exercise in experimental pathology and only secondarily and indirectly a physiological investigation, while the greater the precision with which the course and symptoms of any morbid condition are studied, the more the study becomes a matter of science, a matter of pathology rather than of medicine. In other words, asked as a pathologist to enter into this discussion, I find that all other participants have trespassed into pathological territory. This is one of the penalties of sure advance in our common subject: the pathology of yesterday becomes the medicine of to-day, and I might add, the medicine of to-day yields place to the surgery of to-morrow. But this being the case, so as not to reiterate, I am impelled to make my contribution to this discussion a *resumé* of the results obtained in a branch of pathology which others are not likely to dwell upon. It is in many respects an unsatisfactory branch—a branch capable of testing rather than of originating any theory. I refer to morbid anatomy.

I propose, therefore, during the next few minutes, to lay before you what may be gleaned from the post-mortem room bearing upon this subject of internal secretion. But first it is necessary to call your attention to the very narrow limits of the information to be gained from a study of the gross and fine anatomy of diseased organs in this connection.

Morbid anatomy alone can tell us singularly little concerning alterations in function. The existence of lesions recognisable to the naked eye or under the microscope may support conclusions reached by other means. It can do little more. We know from experiment

[1] Being a contribution to the discussion upon "Internal Secretions," at the Tri ennial Medical Congress, Washington, May 5th, 1897.

that three-quarters of the liver, for example, may be removed from the healthy animal with no pronounced disturbance of the bodily functions, that whenever one-fifth or less of the pancreas is left in the dog it may be weeks before diabetes shows itself, that only when fifteen-sixteenths of the thyroid are removed may the dog succumb. In this enormous reserve of material and force may truly be said to lie the secret of the continued existence of living beings. Thus the mere fact that the greater part of an organ is found wanting by the anatomist, or replaced by tissue of another nature, is not in itself absolute evidence that what remains of the organ is functionless or incapable of meeting the needs of the organism. So long as any considerable number of what may be termed the specific cells of an organ are to be determined we must proceed very cautiously in our reasoning; only when the destruction is absolute or nearly so are we on sure ground. Contrariwise, if the cells of an organ appear very slightly altered, while we are accustomed to argue that there has been but little disturbance of function, it is questionable whether we are justified in this opinion. So also if an organ like the thyroid be markedly hypertrophied, that is not in itself proof positive that there is accompanying increased activity and increased internal secretion. In the thyroid, for instance, the boundary line between pure hypertrophy and overgrowth of adenomatous nature is peculiarly vague. It may very possibly be that a simple adenoma of a ductless gland continues to supply an internal secretion; it is difficult to imagine that gland structure of almost perfect type can be present in the body without affecting the body at large.[1] Nevertheless we have no conclusive evidence that this is the case; hence, it is only after most exact and extensive histological study that we can advance any very secure arguments upon the existence of apparent simple hypertrophy, more especially of the ductless glands. The force of this statement will be seen when we come to discuss the bearing of disease of the hypophysis cerebri.

Another matter that has to be taken into account, one that has until now received scant attention, is the existence of vicarious activity. Because one organ is seriously diseased it does not follow that the organism as a whole exhibits disturbances commensurate with the lesions in that organ; other parts may vicariously fulfil its functions. We have the well known example of total extirpation of so important an organ as the spleen being succeeded for years by good health. Here,

[1] It is noteworthy how frequently in attempting to co-ordinate the anatomical data in the class of diseases now before us we are brought to regard the possibility—nay, probability—that neoplasms are not functionless (as we are too apt to consider them), but afford, it may be an abundant, internal secretion.

presumably, the lymph-glandular tissue in general takes over the functions of the absent organ. There is the compensatory development of the parathyroids in athyrea, and further, the frequent, but not constant co-existence of atrophic disease of the thyroid and hypertrophy of the pituitary to which Boyce and Beadles (1) have more especially called attention. Similarly and curiously we meet with frequent persistence or enlargement of the thymus when either the thyroid or the pituitary body is the seat of disease. Thus not only is it a matter of peculiar difficulty in that class of diseases, which to-day we have specially to discuss, to determine which of the ductless glands is primarily and which secondarily affected, but the added difficulty besets us, that where the vicarious function is perfect and compensation is complete we may, in the apparently unaffected individual, meet with lesions of an organ—the thyroid for instance—of the same nature as, and every whit as extensive as, the lesions in well marked cases of those special forms of general disease which we are inclined to regard as the direct outcome of disease of that organ.

Time after time this co-existence of apparently identical lesions in cases of relative health and pronounced disease places us in a quandary, time after time we find ourselves groping vainly in a maze of facts which seem to point in all directions of the compass. And when the facts flatly contradict each other one cause of discrepancy must be this vicarious activity. In passing I may suggest that vicarious activity affords a possible explanation of the not unfrequent cases in which we have the eventual co-existence of more than one of the diseases under consideration. If, for example, the thyroid be the seat of atrophic disease the compensatory hypertrophy and over-action of the pituitary may lead to eventual affection of that organ.

Yet another consideration, seriously weighing upon the morbid anatomist, is that two opposite processes may produce a similar symptomatology, one that he can recognise, another that he cannot. If the glands afford an internal secretion entering the lymph and so eventtually circulating through the system, we know that the ultimate use of the secretion must be to effect a chemical transformation of some substance in some other part or parts of the system. There are thus four possible conditions, (1) production of an insufficient amount of internal secretion of any gland in consequence of disease of that gland, and (2) the assimilation or production of an excess of that substance which normally is acted upon and transformed by the internal secretion in question. In both cases there will be a heaping up in the system of the substance ; in both cases there may be the same train of symptoms. In the one case the gland or glands may

show the clearest signs of disease ; in the other they may appear normal. The morbid anatomist may in time discover collateral disturbances distinguishing these two states ; at present he cannot adequately. In one case of diabetes he finds the pancreas unaffected, in the next it is extensively diseased. Unaided by experimental pathology he is quite incapable of determining the important *rôle* played by this organ in regulating the sugar supply of the organism and in the production of diabetes. Similarly there may be an accumulation of the internal secretion, either due to (3) hypertrophy of a gland, or (4) not associated with recognizable glandular change.

In short, gentleman, I fear that I stand before you as a kind of reversed contrary Balaam. Summoned to bless—to illumine this discussion—I can only curse (as I take it all my predecessors must have done who have attempted to reconcile the anatomical results in the class of cases now before us) and can but point out to you the darkness that is upon the face of the deep. But happily there is this to be said to the credit of the morbid anatomist that the demonstration of this darkness is of the highest value as indicating the lacunæ in our knowledge and suggesting the various factors that have to be taken into consideration and carefully studied in order that we may gain a comprehensive knowledge of this intensely interesting and valuable subject of internal secretion and glandular function. It is in itself a step towards higher things to feel acutely our own ignorance.

And then, perhaps, things are not quite so black as here painted. While it may be that I am overbold—it may also be that this darkness but precedes the dawn; that facts which seem so flatly to contradict each other can, in the growing light of experimental pathology, already be seen to range themselves in an orderly manner. Accepting the postulates, first, that the glands of the body afford an internal secretion capable of acting upon and transposing some substance or substances produced or assimilated by other regions of the body, and, second that, proceeding with due caution, we can utilise the results of anatomical and histological studies, then, applying the considerations which I have just urged, we must recognise the possible existence of three orders of conditions, each order being capable of further subdivision into two well marked groups.

It would seem that we have to deal with :

Changes Associated with Symptoms of Disease.

I. Relative Glandular Inadequacy.—Excess of substance acted upon by the internal secretion of a gland, without due compensation.

(1.) Altered condition of gland leading to diminished activity and dimished internal secretion.

(2.) No disease or alteration of gland but excessive production or assimilation of the substance acted upon by the internal secretion.

II. Relative Glandular Over-Activity.—Excess of internal secretion without compensation.

(1.) Altered condition of gland leading to increased activity and increased pouring out of internal secretion.

(2.) No disease or alteration of gland, but diminished production or assimilation of the substance acted upon by the internal secretion of that gland.

Changes Unaccompanied by Symptoms of Disease.

III. Compensation.—Lesions of gland or altered systemic condition unaccompanied by symptoms.

(1. Altered condition of gland leading to (*a*) increase or (*b*) diminution of internal secretion, with due compensation.

(2.) (*a*) Increased or (*b*) diminished production or assimilation of substance acted upon by internal secretions, with due compensation.

Let me here emphasise the fact that I do not pretend that this table includes every possible condition leading to local or general disturbance of these glands affording an internal secretion, and leading to the symptoms most often associated with disease of these glands. For example we know from experiments with phloridzin that glycosuria may, among other things, be the result, not so much of increased production of sugar as of increased removal of this body through the kidneys. Such cases are not embraced in this table. Again, what I may term compound cases as, for instance, of glandular inadequacy, in part from disease, in part from increased production of the substance acted upon by the secretions are presented only by implication. All I urge is, that this table, conforming with what experiment has shown may occur, may very possibly be utilised to explain the apparently contradictory revelations of the post-mortem room.

I would now proceed rapidly to review those conditions, local and general, concerning which we have already a modicum of knowledge and which fall within the scope of to-day's discussion.

THE PANCREAS AND DIABETES.

Let me in the first place take into consideration lesions of the pancreas and their relationship to diabetes. Much more than a century has passed since attention was first called to the pronounced changes to be seen in the pancreas in some cases of diabetes. We all

know that not until 1889, when Von Mering and Minkowski in Germany, and de Dominicis in Italy, published the results of their researches did the belief in the existence of a pancreatic diabetes begin to become generalised, but even at the present moment the fact that two cases, closely resembling each other clinically, may post-mortem show, the one, extensive pancreatic disturbance, the other an apparently healthy pancreas, creates great confusion.

What then are the facts gathered so far as to the relative frequency and the nature of the lesions of the pancreas which may be associated with diabetes ?

We have at least three careful studies upon this subject, those of Hausemann (2), Williamson (3) and Dieckhoff (4), and all demonstrate that three conditions may be distinguished (1) extensive pancreatic disease with associated diabetes; (2) extensive pancreatic disease without diabetes; (3) diabetes unassociated with recognisable pancreatic disease. Hansemann from a careful investigation of the records of the Pathological Institute and the Augusta Hospital at Berlin, found that the first condition (of pancreatic disease with diabetes) is more common than the two others combined. It may be that in Berlin the consumption of much beer predisposes to the pancreatic form of the disease, it may be that the material upon which Hansemann worked was imperfect to this extent, that full care was not taken to distinguish between extensive and extreme destruction of the pancreatic tissue, but it will, I think, be the experience here, as it was that of Williamson in England, and Dieckhoff in Rostock, that advanced pancreatic disease, associated and unassociated with diabetes, are to be encountered the one but little more frequently than the other.

This much, howevar, stands out very prominently that where in diabetes the pancreas is found affected, the morbid process within the gland is some one or other form of atrophy and destruction of the gland substance. Most commonly it is a form of periacinous fibrosis, originating it would seem secondarily to arterio-sclerosis, in which with thickening of the arterial walls there is malnutrition of the gland cells, atrophy and, what I have elsewhere termed, replacement fibrosis. Other forms of atrophy and fibrosis have not infrequently been observed—simple atrophy, congenital syphilitic fibrosis, obstruction of the ducts with calculi, dilatation of the ducts and atrophy of the gland tissue, scirrhous cancer of the pancreas, and I have found recorded five cases of necrosis, or hæmorrhagic necrosis (two by Fitz and a third, a case under Drs. Bell and Finley, in my own experience at the Montreal General Hospital)

There can, therefore, be no question that the pancreatic lesions

found in some cases of diabetes are such that there must be a marked diminution in the secretory activity of the gland. To this extent, in this one class of cases the results of autopsies are clearly in accord with the results of experiments. We have here examples of relative glandular inadequacy brought about by altered condition of the pancreas leading to diminution of internal secretion.

Examples of diabetes unassociated with disease of the pancreas are so well known that I need but refer to them. While such are difficult to explain from purely anatomical considerations the fact that they are found, and found relatively frequently is, in itself, an evidence that glycosuria is of at least a two-fold origin. That they are found is in conformity with the results of experiments, experiments which, on the whole, must be regarded as proving that there can be heaping up of sugar in the organism beyond the transforming power of the pancreatic internal secretion, or otherwise an incomplete burning up of the sugar. If this heaping up be in general due to increased glycogenesis, increased production of sugar, we should expect to find some evidence of increased activity of some glycogenetic organ, and here the recent researches of Glénard (5) and Triboulet (6) tend to show that this may be the case. Contrary to the older and generally accepted teaching, Glénard finds that clinically in over sixty per cent. of diabetics, there is evidence of some hepatic enlargement. Anatomically he finds that three conditions may be recognized, each possibly a stage in one morbid procees, namely, hyperæmia, general cellular hypertrophy (hyperplasia) and hypertrophy with cirrhosis (hypertrophic cirrhosis). Thus while I will not say that anatomical considerations prove the existence of my second subgroup in this connection, I must point out that the existence of this class of cases of diabetes without adequate recognizable pancreatic disturbance, is best explained on the supposition that there may be excessive production or assimilation of sugar with accompanying relative pancreatic inadequacy.

There is yet a third group of cases to be considered, that of extensive atrophic disease of the pancreas without diabetes. Here we have to proceed cautiously in our reasoning. As I have already indicated, Sandmeyer (7) has found that if only one-fifth to one-ninth of the organ be left in the dog, it may be months before sugar appears in appreciable quantities in the urine. Vaughan Harley (8) gives an even smaller amount, namely, one-fifteenth, but evidently he refers not to the eventual development of diabetes, but to its onset within a few hours. We can thus state that so long as from one-ninth to one-fifteenth of the glandular tissue of the organ is functional, for so long glycosuria

need not manifest itself in the dog. There is no valid reason why we should not apply these facts to the human being. Hence so long as a very small proportion of fairly healthy gland tissue is left, we have a satisfactory explanation why diabetes should not show itself, even though the major portion of the pancreas exhibits fibroid and atrophic or neoplastic changes. There are, however, aspects of that subject not capable of so simple an explanation. I remember my friend, Dr. H. D. Rolleston, of St. George's Hospital, showing to me a series of sections of the fibroid pancreas taken from both diabetic and non-diabetic cases, from which the only conclusion to be reached was that a given extent of fibrosis might or might not be associated with diabetes. Again, Hansemann has called attention to cases of complete replacement of normal pancreas by a diffuse cancerous infiltration. He seeks to explain these by the hypothesis already indicated, that the cells of a primary new growth of a ductless gland may continue to furnish an internal secretion. This may or may not be the case. Where there is primary cancer of the hepatic parenchyma, the new growth in the liver may be devoid of bile, the secondary growths are without exception free from bile. A more simple explanation of these and other examples of complete or almost complete destruction of the pancreatic glandular tissue is that of compensation, whether by vicarious function of Brunner's and other glands (the duodenal glands have frequently been found enlarged) or by diminished assimilation or production of sugar.

THE SUPRARENAL BODIES AND ADDISON'S DISEASE.

We meet with an identical series of cases in connection with another organ in which experimentally the existence of an internal secretion has been fully demonstrated. We may have (1) Addison's disease associated with disease of the supra-renal bodies, (2) Addison's disease with intact supra-renals, and (3) extensive, if not complete, destruction of the supra-renal bodies without the symptoms of Addison's disease.

Here as with the pancreas in diabetes the affection of the gland in Addison's is some form of atrophy or destruction of the specific gland tissue. Most frequently, I need scarce say, the change is tuberculous and necrobiotic, resulting in the disappearance of the gland tissue and its replacement by caseous material. But cases are on record of simple atrophy, hæmorrhagic necrosis and malignant growth of the bodies associated with or leading to all the symptoms of Addison's disease. In the vast majority of cases both glands are affected, but cases are on record (I have come across one such) where only one of

the bodies has been the seat of recognisable disease. Of the three conditions above mentioned the most frequent found is the association of the disease with complete or almost complete destruction of the gland. So frequent is the association that the attempts to explain away the other two rare states of Addison's disease with intact suprarenal bodies and suprarenal disease without the Addisonian symptoms have been almost painful in their ingenuity. Yet undoubteedly well authenticated cases are on record of both of these conditions.

We have in this connection singularly full statistical collections of cases. That of Lewin (9) is well known; he collected accounts of 285 cases, of which 211 showed caseous lesions of the suprarenals (74 %). Gilman (10) found an even greater proportion of either primary or secondary tuberculosis (80 %); in the remaining 20 % there were either other forms of atrophic disease or absence of recognisable disturbance.

The existence of cases of Addison's disease without obvious disease of the suprarenals is generally acknowledged. Lewin found that as many as 12 % of his cases were of this type. The explanation generally given is that in these there had been alterations in the neighbouring semilunar ganglia and abdominal sympathetic. Certainly disturbance of the nervous system, and especially of the sympathetic, does lead to pigmentation of the skin, We see this in cases of hysteria and again in Graves' disease, in which from whatever cause (I shall speak of this later) we have most marked nervous changes, but I must confess that I feel some little impatience towards the upholders of this semilunar ganglion theory of Addison's disease, for scarce two of them describe the same order of lesions. Most of the changes described would appear to be quite common in the adult dying from other causes; thus Hale White (11) found that examining 33 semilunar ganglia removed indiscriminately, if we leave out of account 3 perfectly normal taken from young children, 24, or 80 per cent of the remainder exhibited more or less extensive degenerative changes with frequent presence of granular masses of pigment. Dixon Mann (12) also making a careful comparative study of the abdominal sympathetics and semilunar ganglia from two cases of the disease and from the unaffected individual came to a like conclusion. He found them not more affected than are those of other individuals. Under the circumstances, therefore, I see no valid reason why cases in which the bodies are found apparently unaffected may not, in the light of our present knowledge, be most satisfactorily classed as possible examples of relative glandular inadequacy of the second order. This suggestion may to some appear revolutionary; but let me reiterate my main argument: We acknowledge that

glands like the suprarenals produce an internal secretion: We must inevitably admit that the function of such secretion is to affect a chemical transformation of some substance or substances distributed in other parts of the body. We must admit that when, for example, the suprarenal bodies are diseased, or removed, some, at least, of the symptoms that follow are due to the absence of the internal secretion, or, in other words, are due to the accumulation in the system of the substance or substances acted upon by the internal secretion. The same symptoms must be produced whatever the cause of the accumulation of the substance or substances, whether by diminution of the internal secretion or by excessive production or assimilation of the aforesaid substance or substances. When, therefore, a morbid condition, such as diabetes or Addison's disease, which may be caused by destruction of a gland is found to exist without recognisable disease of that gland, a very possible explanation of the condition is what I have termed relative glandular inadequacy due to excessive production or assimilation of the substance acted upon by the internal secretion. I would but ask you clearly to picture this, that in diabetes and Addison's disease it is not the internal secretion that causes the symptoms, but, if experimental data are to be trusted, the lack of the same—and that this lack may be absolute or relative.

I am far from suggesting that the whole corpus of symptoms will be the same in both conditions. Thus as Harley and others have pointed out where the pancreas is atrophied there are profound digestive disturbances not necessarily accompanying diabetes unassociated with pancreatic disease. But I am inclined to think that the cardinal symptoms in both will closely resemble each other.

A few words only are necessary concerning affections of the suprarenal bodies without symptoms of Addison's disease. If bronzing be required as the one essential symptom then cases of tuberculous disease of the suprarenal without 'Addison's' are fairly frequent. Addison himself noted this condition. We must however, it seems to me acknowledge with Chvostek (13) and numerous previous observers, that bronzing is but one of a group of symptoms even though we be not prepared to accept Bedford Fenwick's (14) suggestion that bronzing is especially connected with disease of the cortical layer. Leaving this category out of consideration, cases of extensive atrophic or neoplastic disturbance of both suprarenals without Addison's disease are few in number, far fewer than the cases of extensive pancreatic disease without diabetes, and in general the descriptions given are not sufficiently exact to be relied upon. Nevertheless they exist. Greenhow (15) apparently met with a case of almost complete atrophy without sym-

ptoms, and, in 1050 autopsies upon subjects dying from diseases other than Addison's, Rolleston (16) met with an example of caseation of the right and atrophy of the left suprarenal and with three cases (under the age of forty-five) in which both were peculiarly small. All these were without symptoms intra-vitam. There are more frequent examples recorded of cancerous growth destroying both bodies without noticeable symptoms. There is a possibility that the new growth here was so rapid and so recent that symptoms had not time to develop. In the atrophic and tubercular cases it is not so easy to accept this explanation. Therefore, I am inclined to believe that compensation may occasionally manifest itself in man as it does occasionally in animals which have suffered complete ablation of both organs.

THE THYROID GLAND AND MYXŒDEMA.

I have already approached the limits of the time allotted to me and there is yet for me to pass in review the gland and its affections, which in this connection have created the most general interest. I refer to the thyroid and to the conditions of myxœdema, cretinism and exophthalmic goitre.

From an anatomical point of view there is little for me to say in elucidation of the pathology of myxœdema beyond the one all-important statement that, with very rare exceptions, there is discoverable a well marked atrophy of the thyroid. About this all pathologists are agreed. In the majority of cases the atrophy is peculiarly extensive, the specific cells of the gland being replaced by fibrous tissue ; in some it is not so far advanced and areas may be found, not merely of degenerated remains of the vesicular epithelium, but of vesicles which by the superabundant proliferation of their epithelium would seem to be undergoing a compensatory hypertrophy. Yet where these are present they are localised and few in number ; the main mass of the organ shows atrophy. A few cases only are on record, like that of Gulliver (17), where there has been a cancerous metamorphosis or replacement of the parenchyma.

That in these cases the myxœdema is associated with diminished internal secretion of the gland is, I need scarce say, substantiated by the good effects of treatment by thyroid extract or thyroid feeding.

It must next be asked whether myxœdema can show itself with apparently intact thyroid, *id. est*, whether there are any cases which may possibly be explained by excess of the substance or substances acted upon by the internal secretion of the gland. The literature is peculiarly silent upon this point. I can find no example of autopsies upon cases diagnosed clinically as myxœdema in which the gland was

found normal, or but little affected. I can only recall an autopsy upon a patient of Dr. J. Stewart at the Royal Victoria Hospital, in which I found a large cancerous tumour of the pituitary. Here there had been a myxœdematous swelling of the hands, and of other regions to less extent, without bony overgrowth, and no change was found in the thyroid. The condition, however, was not sufficiently advanced to deter Dr. Stewart from diagnosing tumour of the hypophysis. A somewhat parallel case (of apparent atrophy of the pituitary), in which the symptoms of myxœdema were more marked, is recorded by Codd (18), but the anatomical details are given very briefly. Similarly we possess no exact records of atrophic disease of the glands unassociated with myxœdema. I can only point out that it is not uncommon in the aged who show no signs that can properly be regarded as myxœdematous—unless senility itself be regarded as such—to find a condition of very extensive chronic interstitial thyroiditis (as it may be termed) with arterio-sclerosis, calcification and hyaline changes, with retrograde or pseudo-embryonic type of vesicles. I have come across more than one case of this nature. There can be no doubt that here the secretory activity of the gland tissue must be very greatly reduced. If, however, we turn to cases in which by surgical means the equivalent of complete atrophy, namely, complete thyroidectomy, has been attained, we then possess abundant evidence that the thyroid proper may be absent without myxœdema necessarily intervening, and almost as abundant evidence from the more recent researches that the absence of symptoms is connected with vicarious activity on the part of other organs, and especially of the parathyroids. These may be regarded either as true accessory thyroid tissue, or as distinct organs, according to the point of view of the individual. Certainly when the thyroid is functional they do not acquire the full characters of thyroid tissue, but similarly there are often within the healthy organ scattered areas of embryonal tissue. This can be said with precision, that they are independent masses of tissue, apparently most closely related to the thyroid, which are at times capable of development to, or towards, the adult type of the gland, and of assuming vicarious functions. In like manner the pituitary body can at times undergo very definite compensatory enlargement. This was first demonstrated experimentally by Rogowitsch (19), while Boyce and Beadles more especially have added to our knowledge of its enlargement in cases of myxœdema, cretinism and cachexia thyreopriva.

An interesting point in this connection, to which attention has been drawn by Rogowitsch, is that the rabbit, from which the thyroid can

be removed with impunity, has a pituitary body relatively five times as large as that of the dog, in which ablation of the thyroid leads rapidly to symptoms of acute athyrea; or more correctly, the relationship of thyroid to pituitary is 3 to 1 in the former, 15 to 1 in the latter animal.

On the whole, therefore, anatomical data in connection with myxœdema and cachexia thyreopriva support and are capable of explanation by this doctrine that where glands afford an internal secretion, the development or non-development of symptoms of disease depends primarly upon the relative amount of internal secretion produced and of the substance or substances acted upon by the same.

CRETINISM.

Cretinism presents a far more complicated histologic l picture—so complicated that Bircher (20) argues with very considerable force that "cretinic degeneration, as also dwarfism and chondrodystrophia fœtalis hypoplastica have no ætiological connection with the functions of the thyroid," Bircher, however, fails to recognize that if we accept the existence of an internal secretion, we must also admit the presence of substances upon which that acts, and he cannot see that widely contrasted anatomical conditions may lead to the same train of symptoms. We must, I think, abide by the experimental and clinical evidence that removal of the thyroid in the young leads to a condition undistinguishable from cretinism. This being so, we find that in some few cases of typical cretinism the thyroid is completely absent, in a large number it is small, in a yet smaller number according to Von Eiselberg (21) and Kocher (22) there is a goîtrous condition present, while according to Bircher the goîtres may be of all possible forms, from simple hyperplasia through soft (parenchymatous) and cystic to fibroid. The only point clearly to be made out from Bircher's very destructive criticism is that while in several cases the thyroid has been found of normal size, apparently no case exists in which by microscopical observation it has been found of normal structure. Considering the amount of material he brings forward this is rather remarkable. I further gather that his statements as to the frequency of the various forms of goître are based upon examination of the living and not upon post-mortem or surgical material. This seriously weakens his case. Beyond this I will not venture to travel. Bircher's statements require to be dealt with by one in authority, and I await with interest Dr. Osler's presentation of the matter.

EXOPHTHALMIC GOITRE.

I will now briefly refer to the condition which presents a series of symptoms so remarkably contrasted with myxœdema—which also

anatomically presents an equal contrast. There is to be found in exophthalmic goître, as Greenfield (23) has shown, and as is now generally accepted a characteristic hyperplasia of the thyroid parenchyma, complicated, it may be in later stages, by increased fibrosis. The one question of immediate concern here, is whether from this we can safely deduce that there is accompanying increased internal secretion. As I have already hinted, I do not think that from anatomical considerations alone we can safely make this deduction. There is, however, an important fact in favour of such deductions, namely, the strong likeness between the primary glandular changes in Graves' disease and those described by Halsted (24) and others as occurring in the compensatory hyperplasia of the thyroid after removal of large portions of the gland; and if, together with the anatomical changes, we consider the favourable effects which so often follow removal, destruction, or diminution in the blood supply of portions of the hypertrophied gland in this disease—of operations which must lessen the internal secretion—it is difficult to arrive at any other conclusion than that in exophthalmic goître there is increased internal secretion, and that this plays a singularly important part in the development of the symptoms. Whether this be primary or secondary to lesions of the central nervous system—of the restiform bodies for example, our present anatomical data are insufficient to decide—as again they are incapable of deciding whether the increased secretion is altered or unaltered in quality. I may here note that as Joffroy and Achard (25) have indicated the symptoms of parenchymatous and adenomatous goître are at times curiously allied to those of exophthalmic goître. Indeed, together with Vanderwelde and le Bœuf, they hold, I think without due cause, that there is nothing anatomical to distinguish the one condition from the other. That the one condition may lead to the other is a matter of clinical experience. As Dr. Shepherd has pointed out to me extirpation of the goîtrous nodules or cysts leads to the almost immediate amelioration of the symptoms.

The development of exophthalmic goître without hyperplastic alteration of the thyroid is a matter concerning which there is little anatomical evidence. I find one case recorded by Joffroy and Achard in which the gland was of normal size and, while not normal histologically, presenting nevertheless a series of changes wholly distinct from Greenfield's classic description. The vesicles instead of being small and corrugated, were enormously distended, instead of absence there was abundance of colloid material, in place of a columnar and proliferating epithelium, the lining cells were flattened. Not a few

believe in the existence of Graves' disease without goître. Among recent writers Buschan (26) especially holds this view, but save in the above case I cannot find anatomical substantiation for the opinion. Clinically Graves' disease without enlarged thyroid has very frequently been noted ; in some cases enlargement supervenes, in others it does not, but there may well be increased activity of the gland without marked enlargement. All that can be said at present from this evidence is that apparently the condition does occur. So also evidence as to the occurrence of marked hyperplasia and presumably increased secretion without symptoms is not so full and precise as could be wished. I can only point out that if adenomatous nodules in the thyroid produce any internal secretion then, while many cases of adenomatous goître show a train of symptoms somewhat allied to exophthalmic goître, and while a few cases pass on to undoubted Graves' disease, many on the contrary appear to last for years without symptoms. And in autopsies upon those dying from diseases, other than exophthalmic goître, we find a wide variation in the condition of the thyroid, from atrophy on the one hand to a condition not far removed from what Greenfield and others describe in association with exophthalmic goître.

Altogether, therefore, while not prepared, from general as from anatomical considerations, to state positively that exophthalmic goître is in all cases primarily due to increased thyroid secretion, I cannot but admit upon the whole that the facts can be best reconciled by assuming the existence of relative increase in glandular activity.

THE PITUITARY BODY AND ACROMEGALY.

Finally some few words must be said concerning that strange collection of symptoms and anatomical changes to which Marie has given the name of acromegaly. Yearly it has become more clearly recognized that the term indicates a definite disease although there is a liability towards confusion with gigantism on the one hand, and on the other with the remarkable overgrowth of bone in certain cases of chronic disease (mainly of the lung) which again Marie was the first to group together under the title—voluminous, and in other respects unsatisfactory—of hypertrophic pulmonary osteoarthropathy.

Here again the remarkable trio of conditions forces itself upon our notice ; there may be acromegaly with disease of the pituitary, acromegaly with apparently unaffected pituitary and extensive disease of the pituitary without acromegaly. Where there is acromegaly, there in by far the greater number of cases the glandular portion of the body is diseased. It is true that the condition is rare. Between 1890.

and the present time less than thirty affected subjects have undergone post-mortem examinations. Leaving aside from lack of time sundry interesting observations upon the state of the thyroid and thymus, I may say that this one gland alone—the pituitary—has been repeatedly found altered, the alteration being especially in connection with its anterior or glandular portion. Out of 24 necropsies upon cases stated to be acromegaly, Tamburini (27) the latest collector, finds that in 17 or over 70 per cent. the pituitary has been found diseased. The remaining 7 are subjected by Tamburini to severe criticism with the result that he rejects 2 on the ground that the condition had only been recognised clinically for a few months and no microscopical examination had been made. He presumes that time had not been sufficient for the development of naked eye changes. Three other cases he holds to have been osteoarthropathy. There remain two which he could not definitely reject and consequently classified as doubtful. So far as I can follow Tamburini he is strongly of opinion that morbid changes in the hypophysis cerebri are essential to acromegaly. The majority of observers do not accept this extreme view, and with them I am inclined to believe that here as certainly obtains in diabetes and Addison's disease, there may be typical symptoms without recognisable involvement of the pituitary.

But granting this much, that in the majority of instances the gland is diseased, it is difficult to advance much further, for there is a curious discord concerning the exact nature of the alterations in the pituitary body. In about one half of the cases hypertrophy of the organ is described. Stroebe, (28) Tamburini, Boltz (29) and others of later date conclude that the change is adenomatous, Marino (30) Dallemagne (31) and Gauthier (32) describe a peculiar cystic degeneration, Boyce and Beadles a cystadenoma, while in another of Dallemagne's cases and in Wolf's (33) there was clearly sarcoma, and in Bury's (34) a 'glioma.' What are we to conclude? Is acromegaly accompanied by an increased pouring out of internal secretion, or the reverse? Mere hypertrophy and possibly adenomatous overgrowth might lead to increase, but surely degenerative changes and sarcoma can have no such effect.

It is difficult to reason by analogy, and if we attempt this and seek to base any argument upon what occurs in disease of the gland, which anatomically is most closely related to the pituitary—namely, the thyroid—we are led rather to the conclusion that acromegaly must be due to arrest of function of the former. That is to say there is a certain correspondence between the changes occurring in the connec-

tive tissues in myxœdema and those affecting the bone, and to some extent the subcutaneous connective tissues in acromegaly.

On the other hand, the pituitary is nearly always found enlarged and hypertrophied in general gigantism as distinguished from this localised acromegalic gigantism. It is difficult to reconcile such general gigantism with diminished activity on the part of the enlarged hypophysis, while again the contrast may be pointed out between gigantism and cretinic dwarfism. Tamburini, and independently Massolongo (35) have attempted to coordinate the contradictory anatomical discoveries by suggesting that two stages of the disease may be recognised, a first in which the hypohysis undergoes hypertrophy, and is in over-action, which may give place to a second in which the hypertrophied tissue either undergoes atrophy or adenomatous or sarcomatous change. The suggestion is seductive, but for the present must be regarded merely as a suggestion.

Briefly therefore, our knowledge in this connection is miserably inadequate, and experiments have so far been without result. We cannot say whether in acromegaly there is increased or diminished internal secretion. While the change in the pituitary appears often to be primary, we cannot with certainty lay down that this is the case. It has only to be added that if we admit that lesions of the pituitary are associated with acromegaly, we must also admit that compensation can occur, for there is considerably over a score of cases on record of hypertrophy, adenoma and cystadenoma of the organ, all of considerable size and presumably of long duration which had developed without signs of the disease in question.

Thus to conclude a long discourse, which in justice to the subject I could not well shorten: I have here, gentlemen, followed a single train of thought. Some may find it suggestive, to some it may be so simple as to be specious, so wide in its embrace that its very comprehensiveness is its damnation. I can only point out that which is here written has been already more or less definitely suggested by various writers in this country and elsewhere, in connection with most, if not all, the conditions here discussed, and impress upon you that, if we are prepared to accept the results of experimental research and to believe in the existence of internal secretions, then, inevitably, we must be led to some such views as those brought forward in the course of this paper.

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