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ON

THE DIAGNOSIS AND TREATMENT OF
SOME DISEASES OF THE ENDO-
CRINE GLANDS.

BY

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ENDOCRINOLOGY is one of the younger branches of medicine, but it has grown so rapidly of recent years that there are already several textbooks devoted to the physiological, pathological, and clinical aspects of the subject, and the Association for the Study of Internal Secretions in America publishes a quarterly journal entirely devoted to this subject. A brief consideration of the early diagnosis and treatment of some of the diseases of the endocrine glands in the light of our present knowledge will, therefore, be of interest to you. Time will not permit of a consideration of the special physiological action of these glands, but, speaking generally, it may be said that each forms a secretion containing one or more hormones, which are carried by the blood to the tissues. Each hormone has a special influence upon growth and development in the young and upon general metabolism throughout life. The symptoms of disease of an endocrine gland are therefore due either to changes in its size causing pressure upon surrounding tissues, or to alterations in its functional activity leading to an increase or decrease in the supply of hormones, or possibly to an alteration in their character. Thus, for example, in the case of the thyroid gland symptoms may be due to the pressure exerted by an enlarged gland upon the neighbouring structures, or they may be the result of hyperthyroidism, hypothyroidism, or dysthyroidism. Changes in size and function often occur together, but we may have great change in size without obvious alteration of function, or we may have marked change in function associated with but slight change in size.

THYROID GLAND.

It is somewhat remarkable, at a time when the importance of the diseases of the endocrine glands is fully recognized, that little, if any, mention is made in textbooks devoted to clinical diagnosis of the methods of either examining these organs or of estimating their functional activity. In other branches of medicine the tendency in the past has been rather to devote a great deal of care to the physical examination of diseased organs, while too little attention was paid to the study of the early symptoms which indicate change or failure in functional efficiency. Diseases of the endocrine glands have, however, generally been recognized by observing symptoms which result from alterations in their functional activity, and not by physical examination. In the case of the thyroid gland, at any rate, much may be learnt by a careful physical examination conducted on similar lines to those we follow in examination of other internal organs, such as the lungs. We may with advantage shortly consider the application of these familiar methods of examination to the investigation of the condition of a diseased thyroid gland and the information which may be obtained by their regular use in the examination of patients suffering from maladies of this gland.

On inspection in a good light any marked enlargement of the thyroid gland will at once be noted. In the case of a uniform parenchymatous enlargement the swelling in front of the neck is seen to retain the normal shape of the gland, the right lobe being usually larger than the left. When the size and shape of the swelling have been fully observed, the patient should be asked to swallow. During the act of deglutition the enlarged thyroid will be seen to rise and fall with the larynx and trachea. It must, however, be remembered that there are exceptions to this rule. Rarely, a tumour which is not of thyroidal origin, such as a tuberculous gland, a lipoma, an abscess or a sebaceous cyst, may become adherent to the larynx or trachea, and by moving with them simulate a goitre. On the other

hand, a goitre may be prevented from moving owing to its large size or to fixation to surrounding structures. This fixation occurs in cases of malignant goitre, or it may be due to the presence of inflammatory adhesions. In a case recently seen an elastic swelling, about the size of a walnut high up in the neck, which was thought to be a branchial cyst, on removal turned out to be an enlarged accessory thyroid gland.

Slight uniform enlargement of the gland is common in young women, and it has certainly become more noticeable since the introduction of the modern fashion of wearing dresses which leave the front of the neck exposed to view. It has been thought by some that this form of enlargement has actually become more frequent of late. I do not, however, know of any reliable observations as to whether this enlargement really occurs oftener now than it did before the war. In some people an apparent fullness of the front of the neck is caused by two parallel creases in the skin crossing the front of the neck at about the level of the upper and lower poles of the lateral lobes of the thyroid gland with a layer of subcutaneous fat lying between. It will, however, be easily noted that this fullness extends laterally beyond the limits of the gland and does not move with deglutition. Irregularity in the outline of a goitre due to the presence of adenomata or cysts within it are obvious on inspection. Any distension of the external or internal jugular veins by the pressure of a goitre will also be noted on inspection.

On palpation of the front of the neck, except in fat persons, the size of the thyroid gland can usually be approximately determined. When it is atrophied the rings of the trachea can be more distinctly felt than usual and the finger can be pressed in on each side of the trachea to a greater extent than when the gland is of normal size. Any slight increase in size of the gland which may be regarded as pathological can be detected more easily than by inspection alone. Larger goitres can be more fully examined and the presence of an adenoma or cyst, unless deeply seated, can usually be determined. At the same time the position of the larynx and trachea should be determined as accurately as possible so as to ascertain if they are displaced to the right or left of the middle line. It is often difficult to distinguish between an adenoma and a cyst. Both are smooth and rounded in outline, and a tense cyst may feel like a firm adenoma, or an elastic adenoma may feel like a cyst. On careful fixation by the tips of four fingers fluctuation may be felt in a cyst which is absent in an adenoma. A reliable and simple method of recording the size of an enlarged gland is desirable. The following measurements are helpful but cannot be relied on to indicate slight changes in size: The circumference of the neck over the isthmus or most prominent part of the goitre; the transverse measurement of the goitre from the outer border of each lobe and the vertical measurement of each lobe separately. The transverse diameter of each adenoma or cyst may also be recorded. Thrills, which are frequently present in cases of exophthalmic goitre, are easily detected on light palpation of the goitre.

Percussion of a goitre is not often employed, but may yield valuable information in certain cases in helping to determine the position of the trachea or the presence of gas in a cystic adenoma. It is often important to determine the position of the trachea in relation to a unilateral or asymmetrical goitre so as to ascertain if it is displaced from the middle line. Careful light percussion on the left forefinger laid on the front of the neck, parallel to the long axis of the trachea, will often yield a tympanitic note when it is immediately over the windpipe. Finger-tip percussion may also be employed, the terminal phalanx of the left forefinger being flexed as nearly as possible at a right angle, so that the tip of the right middle finger may strike on the terminal interphalangeal joint as nearly as possible in the direction of the long axis of this terminal phalanx when it is placed on the front of the neck. Sanson's pleximeter may also be employed in percussing out the position of the trachea, the long arm being placed in a vertical position over the left edge of the goitre and gradually moved across the front of the neck until the tracheal note is obtained. The presence of gas in a cystic goitre is a rare occurrence, but it may easily be overlooked if a goitre is not percussed. Gas in such a situation can only be detected by percussion or by x-ray examination. Several years ago I saw a striking example of this with

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Dr. Albert Hopkinson. The patient was very ill, with a high irregular temperature and other indications of an acute toxæmia, for which there was no obvious cause. He had a large cystic goitre, which had been present for a long time without causing any special inconvenience. In the course of the examination of this patient the goitre was percussed and yielded a resonant note. As no other source of infection was found, we came to the conclusion that the cystic goitre had become infected by the *Bacillus coli communis*, which, being a gas-forming organism, had caused the formation of gas in the cyst, and that this infected cyst was the source of the man's acute illness. Drainage of the cyst was advised. This was done, and at the operation the cyst was found to contain gas and pus with the characteristic smell produced by *Bacillus coli*. After the operation the patient made an uninterrupted recovery.

Auscultation of the trachea is useful in cases of goitre in order to ascertain the presence and degree of compression of the trachea. In auscultation of the trachea the chest-piece of either a single or double stethoscope is placed over the front of the trachea between the cricoid cartilage and the upper end of the sternum. The loudness and character of the tracheal breath sounds normally vary considerably in different individuals, so that it is advisable to be familiar with the sounds as heard in a number of healthy persons. When the trachea is compressed by a goitre the breath sounds become higher pitched, and are as distinctly audible during expiration as during inspiration. If the compression is marked so that the trachea is much narrowed the breath sounds are stridulous in character. The amount of change from the normal serves as a useful indication of the amount of narrowing which has taken place. The alteration in the sound as normally generated by the passage of air between the vocal cords is probably due to the passage of the air through the constriction caused by the pressure of the goitre. The degree of compression does not of course depend on the size of the goitre. The largest goitre I have seen did not compress the trachea, as its weight dragged it downwards on to the upper part of the chest. On the other hand, quite a small retrosternal goitre may cause urgent and dangerous dyspnoea owing to the lack of space for expansion in this situation. In a case of "ligneous thyroiditis," recorded by Mr. F. A. Southam and myself,¹ there was urgent dyspnoea necessitating operation, although the enlargement of the gland was only moderate, and microscopical examination of the portion which was removed showed that the glandular structure had been replaced by dense fibrous tissue. Auscultation of the enlarged gland in Graves's disease frequently reveals the presence of murmurs. A continuous venous murmur or a systolic murmur synchronous with the pulse in the thyroid arteries may be audible.

Examination by x rays may be employed in some cases to determine the size and position of the trachea and for the detection of a retrosternal goitre. By the systematic examination of the thyroid gland just described we can obtain a good deal of useful information as to its size, shape, and relationship to important neighbouring structures, such as the trachea, but physical examination alone tells us but little as to the functional activity of the gland, which in many cases is much more important than its size or shape. The functional activity of an endocrine gland can be roughly estimated by a careful consideration of the clinical symptoms and signs presented by the patient when the normal supply of hormones is either increased or decreased owing to structural changes in the gland. Further information can be obtained by estimating the changes in metabolism which occur in these maladies by the more accurate methods of the laboratory which are gradually coming into use. It will be useful first to consider the clinical indications which enable us to determine, at as early a stage as possible, that a patient's symptoms are due to disease of an endocrine gland. The symptoms caused by marked increase of the activity of the thyroid gland, as seen in fully developed Graves's disease, are well known. The symptoms of failure of function as seen in myxoedema and cretinism are characteristic. Owing to the gradual onset of these symptoms their true nature is apt to remain unrecognized too long in some cases. In order to obtain full success in the treatment of the maladies in which the functional activity of the gland is abnormal it is most important that the change should be recognized at the earliest possible stage. When the gland

becomes overactive an excess of thyroidal hormone passes into the blood and metabolism is increased, and it will be useful to consider the symptoms which occur during this period of simple hyperthyroidism when obvious enlargement of the gland may or may not be present. It must be remembered that such hypersecretion may develop in a thyroid gland which has previously been normal in size or in one which has been visibly enlarged for a longer or shorter period without causing any general symptoms. A goitre which is accompanied by some of the symptoms of hyperthyroidism may conveniently be described as a toxic goitre. All grades of hyperthyroidism occur, from slight forms of toxic goitre up to the most severe and fatal forms of Graves's disease, and no sharp division can be drawn between them.

When we inquire into the early history of a case of Graves's disease, it will often be ascertained that for some time prior to the appearance of any well recognized symptom of the malady there has been a period, extending over several weeks or months, during which the patient experienced a constant sense of fatigue. This symptom is present in the early stages of so many cases that it may be considered one of the earliest symptoms of hyperthyroidism of gradual onset. It is probably due to the increased metabolism of the tissues, and may be compared to the exhaustion which is experienced during the ambulatory stage of a fever of gradual onset. At the same time there may be a gradual but progressive loss of weight, even when more food than usual is being taken, owing to the increase of appetite, which is not uncommon at this early stage. Another early symptom is a change in disposition. This is shown by restlessness and a tendency to be agitated or worried by things which previously would have passed almost unnoticed. There may be marked mental depression, or periods of depression or anxiety may alternate with those of agitation. A fine tremor can usually be seen or felt in the hands when the patient extends both arms with the fingers fully spread out. During this early stage there is a slight persistent acceleration of the pulse rate by ten or twenty beats a minute, so that the frequency, even at rest, is raised to 80 or 90. The heart responds too readily to slight exertion or emotion. In order to appreciate this the pulse should be counted when the patient is sitting or lying down, when standing, and after some definite effort, such as stepping up on to a chair five times in fifteen seconds. It will generally be found that either standing or this simple exercise causes an acceleration of twenty or more beats a minute, and that it takes more than half a minute for the pulse to fall to its former frequency. In some cases the patient is conscious of the accelerated pulse rate, or complains of palpitation under the influence of exercise or emotion. It is naturally important in these cases to exclude as far as possible other causes of cardiac irritability before coming to the conclusion that it is thyroidal in origin. When the above symptoms alone are present they indicate hyperthyroidism. If they are associated with an enlarged thyroid gland they indicate a toxic goitre. At the stage we are considering no exophthalmos is present, but the patient may have a somewhat staring or startled expression which is due to a widening of the palpebral fissure caused by slight spasmodic contraction of the elevator of the upper eyelid. At first this sign may be unilateral, and even when it is bilateral the palpebral fissure may be obviously wider on one side than the other. The elevation of the upper eyelids may at first only take place when the eyes are suddenly directed to the right or left, so that the widening of the palpebral fissure is only present for a second or two, after which the upper eyelids fall to their normal position. A slight increase in moisture of the skin, especially of the hands, is perceptible in many cases. Any former tendency to chilblains or chilblain circulation is diminished, or may disappear altogether. In this connexion it is interesting to remember the value of thyroid extract in the treatment of these conditions. In those who are prone to suffer frequently from common colds this tendency diminishes as thyroidal activity increases, only to return when the hyperthyroidism ceases. When these symptoms are present there may be no obvious goitre, though it is usually found on making a careful physical examination of the thyroid gland that it is appreciably enlarged. It is, however, quite possible, though unusual, for a gland which is not apparently larger than normal to be suffi-

ciently overactive to produce the symptoms already mentioned.

I wish to emphasize the importance of recognizing these early stages of the malady, as it is at this period that treatment is most effective, and a long illness may be prevented or curtailed by its prompt application while the symptoms are not yet fully developed. It is to those engaged in general practice that we must look for the detection of these early cases and for the observation of other early symptoms and signs which may occur during this period of the evolution of the malady. After this stage has been reached the pulse rate increases, the thyroid becomes obviously enlarged, the tremor of the hands is easily seen, and exophthalmos may or may not appear, and the disease becomes easily recognizable. A more accurate estimation of the amount of derangement of the gland may be made by a determination of the basal metabolic rate of the patient, as this is increased in hyperthyroidism and decreased in hypothyroidism. This method has been employed in the Mayo clinic by Dr. Irene Sandiford² with interesting results. After twelve hours' fast and twenty minutes' rest in bed, all the expired air is collected in a gasometer for a given period of time. The amounts of carbon dioxide and oxygen in it are then determined by means of the Haldane gas analysis apparatus, the total amounts of oxygen absorbed and of carbon dioxide produced in one hour are determined, and the total heat production ascertained. The total number of calories per hour is divided by the surface area, which varies according to the patient's height and weight. The number of calories for each square metre of the body surface is then compared with the normal. The basal metabolic rate is then expressed in plus or minus percentages according as the production of heat is greater or less than normal. In severe cases of exophthalmic goitre the basal metabolic rate may be as high as 100 per cent. over normal, while in advanced myxoedema it may fall to 40 per cent. below normal. The determination of the metabolic rate has proved of value in distinguishing between true hyperthyroidism and a neurosis simulating it, and it is also a useful index of the improvement resulting from treatment. Thus it was found in thirteen out-patients that the average metabolic rate was +59 per cent. and the average pulse rate 115. After rest in bed for about a week the average metabolic rate fell to +46 per cent. and the average pulse rate to 108. In a group of 22 severe cases of exophthalmic goitre treated by operation at the Mayo clinic the average basal metabolic rate was +66 per cent. and the pulse rate 123. After rest in bed and two ligations of the thyroid arteries the metabolic rate fell to +46 per cent. and the pulse to 115. After three months' rest at home the metabolic rate was +39 per cent. and the pulse rate 107. After subsequent thyroidectomy the metabolic rate was +16 per cent. and the pulse rate 89. In three cases the total result of the treatment was an average fall of 50 per cent. in the metabolic rate and a diminution of 34 in the pulse rate. Further investigations on these lines may render valuable assistance in the recognition of these early stages of hyperthyroidism. In severe cases of Graves's disease glycosuria may be present and the sugar tolerance is lowered, but in early cases the determination of sugar tolerance is not likely to be of much practical value.

As soon as a condition of hyperthyroidism or toxic goitre is recognized treatment must be undertaken, as these early cases are so much more amenable to treatment than those in which the fully developed Graves's disease is present. Rest in bed is advisable for a few weeks, after which twelve to sixteen hours a day should suffice. A liberal diet consisting of milk, fats, and carbohydrates should be regulated according to the necessities of each case. Red meats and meat extracts should be avoided, as they tend to stimulate thyroidal secretion. In these early cases treatment by radium or x rays is of considerable value. As a rule x rays have been used in my cases, when they can conveniently be applied at short intervals, and radium when long intervals between the applications are desirable on account of the distance to be travelled from home. In the use of x rays a large dose is given as can be tolerated without injury to the skin. Dr. A. E. Barclay, who has treated many of my cases, employs from one to one and a half Sabouraud units measured before filtration, and then passed through 3 mm. of aluminium and a layer of boiler felt on the skin. This dose is repeated twice a week

for the first few weeks, after that once a week, and later on at lengthening intervals according to the requirements of the case. The radium treatment has been carried out by Dr. A. Burrows at the Manchester Radium Institute by the application of plates, of a strength of 2.5 milligrams or millicuries to the square centimetre, over the enlarged gland. The plates were of such size that 45 to 76.5 milligrams were applied each time, screened by 1.5 millimetres of lead. The plates were applied for twenty-four hours about once every six weeks. In early cases radio-therapeutic treatment for three to six months may suffice, whereas in fully developed cases it may be necessary to continue it for one or even two years in order to obtain its full effects.

If these methods of treatment are not available the daily application of a mild faradic current by electrodes applied over the goitre and at the back of the neck for an hour twice a day may be used instead. Many drugs have been employed, but arsenic given in small doses for several months at a stretch has given the best results. No consistently good results have been observed after the use of organic extracts, with perhaps the exception of suprarenal gland. With the exception of fresh milk from a thyroidless goat, the various preparations made from animals after thyroidectomy have not fulfilled their promise. The various crises and complications which occur in Graves's disease require treatment which is largely symptomatic.

The recognition of the early signs of thyroidal deficiency in infants and young children is of vital importance as delay in the commencement of treatment may cause such arrest of development as can never be fully made good. One of the earliest signs of cretinism is a delay or arrest of normal growth, and this should at once lead to a careful search for other signs of the malady. Lack of the normal activity may be noted by the mother along with a tendency to coldness of the extremities and dryness of the skin. At this early stage the child will not have the appearance of a typical cretin, but slight thickening of the subcutaneous tissues, especially of the face, neck, supraclavicular fossae, and backs of the hands, may be discernible. The bridge of the nose may be slightly depressed and the complexion is pale. On examination of the neck the thyroid gland will be found to be too small, or absent. The maladies which may be mistaken for cretinism are mongolism, achondroplasia, and rickets. When there is difficulty in making a diagnosis it is advisable to treat the patient as a cretin. If decided improvement soon takes place the diagnosis of cretinism is clear. In an early case a small dose of one of the preparations should be given each night. In a child under one year it is advisable to begin with a dose of 1 minim of liquor thyroidei or half a grain of dry thyroid powder and gradually increase it up to double or treble this amount during the first three weeks of treatment. Subsequent doses must be regulated according to the effect produced. In older children larger doses may be given from the beginning. In any case gradually increasing doses will be required as the child grows older so as to supply sufficient hormones to maintain the basal metabolic rate at the level necessary for full development to take place. In the adult, symptoms of thyroidal insufficiency are apt to appear between the ages of 40 and 50, and less frequently earlier or later than this period. As they are much more frequent in women than in men they are apt to be attributed to the changes in the ovary which occur at this time of life. As the thyroidal hormones diminish the basal metabolic rate falls and the patient complains of gradually increasing loss of energy. Greater voluntary effort is required to initiate any action and more time is taken up in its execution. This is shown in a slowness in response to questions, which are, however, answered correctly. Some patients, though conscious of their difficulties, continue for a time their usual occupations, others soon begin to limit their sphere of action and tend more and more to lead a sedentary existence. The memory may become defective, especially for new names and recent events. Sensitiveness to cold and ill-defined visual and auditory sensations or even hallucinations may be present. The temperature may be slightly subnormal. Slight myxoedematous swelling of the subcutaneous tissues can usually be detected. At first the slight fullness of the face, combined with the pink flush in the cheek may give a false impression of good health to the patient's friends.

Careful inspection of the eyelids, of the supraclavicular fossae and of the backs of the hands will generally show the true nature of the swelling. The skin becomes drier and perspiration occurs less frequently than before. A fine powdery desquamation occurs especially on the legs, and the hair becomes thinner on the head. The thyroid gland will be found to be diminished in size though it is not as yet shrunken as in fully developed myxoedema. It is much easier to supplement a deficient thyroid gland than it is to control one which is overactive, so that the treatment of these cases presents no difficulty once their true nature is recognized. Two or three grains of dry thyroid or five minims of liquid thyroid extract given each night will usually remove the symptoms in the course of a few weeks, though in some cases larger doses may be necessary. The daily dose must, of course, be continued for the rest of the patient's life, and it may have to be increased as time goes on, owing to the progressive atrophy of the gland and further diminution in its secretion of hormones. In time this may fail altogether, so that the patient is entirely dependent on external sources for an adequate supply of thyroidal hormones to maintain the basal metabolism at the normal rate. Advanced cases of myxoedema in which the symptoms have been present for years without suitable treatment unfortunately still occur, as I have seen two recently; both of them rapidly recovered when treated with preparations of the thyroid gland. In such cases the dose should be soon increased up to 10 minims of the liquid extract once a day, which usually suffices to keep the patient free from symptoms of the malady as long as it is continued. As an illustration of the long period for which health can be maintained by this means, it may be mentioned that the first case of myxoedema treated by thyroid extract, whose life-history I recently recorded,⁸ lived in good health for over twenty-eight years, and only died last year from cardiac failure at the age of 74.

Thyroid extract has, however, other uses beyond the supplemental treatment of thyroidal deficiencies, which may be shortly considered. In the treatment of obesity it was expected to be beneficial, but it must be used with caution, and is of little service unless combined with dietetic and other measures directed to the reduction of excessive weight. In the treatment of some diseases of the skin, and especially in some cases of psoriasis, as was shown by Dr. Byrom Bramwell, the stimulating effects of the thyroidal hormones on the metabolism of the skin have a marked influence upon the course of the malady. In the treatment of chilblains I have found this influence of great value, and that it is increased by the simultaneous use of calcium salts.

PITUITARY GLAND.

The diseases of the thyroid gland have been considered first as they serve best to illustrate the principles which should guide us in the diagnosis and treatment of diseases of other endocrine glands. The pituitary gland is so inaccessible that no direct examination is possible. By the use of x-rays a skiagraph may be obtained of the sella turcica, in which it lies. This gives useful information when there is a gross change in size, but is of little help in the early stages of either hypertrophy or atrophy of this gland. Owing to the confined situation of this gland any marked enlargement produces definite effects, which have been called "neighbourhood symptoms" by Cushing, so as to distinguish them from "glandular symptoms" due to changes in functional activity, so that in some cases tumour symptoms predominate and in others the glandular symptoms. When the hypophysis is large enough to cause pressure on surrounding structures the sella turcica is expanded and the patient complains of temporo-frontal headache, the fields of vision are diminished, and there may be partial bitemporal hemianopia and oculo-motor paralysis. Epistaxis and anosmia may also occur. These symptoms are mechanical in origin and occur independently of any glandular symptoms, just as in the case of the thyroid gland. The fully developed effects of prolonged hyperpituitarism, as seen in acromegaly in the adult and one form of giantism in the adolescent, are striking and well known, but it is much more difficult to recognize the early symptoms of overactivity of the hypophysis. Once the characteristic features of acromegaly have developed they remain permanently, although the gland may be no longer overactive, so that operative treatment at this stage at the

best can only relieve pressure symptoms. If any treatment is to be effective it must be applied during the early stages of the malady, and it is for the symptoms of this stage we must learn to look. Dr. Leonard Mark⁴ has given a good account of these symptoms as observed in his own case from the beginning up to the fully developed stage of the disease. The symptoms in his case first began to develop some thirteen years before their true nature was recognized. The earlier symptoms may be drowsiness, sense of fatigue, depression, post-nasal catarrh, and photophobia. To these sooner or later may be added the tumour symptoms already mentioned. The posterior lobe of the hypophysis influences metabolism, and it is probable that some of the early symptoms are due to the overactive stimulation of certain metabolic changes. Overactivity of the anterior lobe stimulates growth of the skeleton and cutaneous tissues. One of the earliest signs of this abnormal growth is the gradual advancement of the lower jaw until the lower incisors project in front of the upper, and biting the food is difficult. At the same time the nose and supraorbital ridges increase in size, and later the tongue becomes larger. Similar changes occur in the hands and feet, but these are difficult to recognize in the early stages unless the patient finds that he actually requires larger boots and gloves than formerly. The sugar tolerance may be diminished and there may be actual glycosuria. Thus acromegaly results from hypertrophy with hypersecretion of the pituitary gland, just as Graves's disease is due to hypersecretion of the thyroid gland. It is significant that both these maladies may occur simultaneously, but I have never seen myxoedema combined with acromegaly, nor Graves's disease with adiposogenital dystrophy, so that overactivity of one of these glands is rarely, if ever, combined with loss of activity of the other. It is true that there is some enlargement of the pituitary gland in myxoedema, but this is probably a compensatory change, as there are no special symptoms referable to it.

The treatment of acromegaly is unsatisfactory. X-ray treatment of the enlarged hypophysis has greatly relieved the headache in some of my cases, but no other definite effect has been obtained. In an early case Dr. J. H. D. Webster⁵ has observed disappearance of the headache, marked diminution of the depression and irritability, decrease of weight, improvement in the fields of vision, and return of the discs almost to a normal condition, though the symptoms returned later after the treatment had been discontinued. The results so far obtained warrant a prolonged trial of x-ray treatment in the early stages of the disease in order to check further enlargement and overactivity of the hypophysis. Surgical treatment is only advisable when the symptoms indicate that the intracranial pressure must be relieved so as to save the vision or relieve an intolerable headache. Treatment by any form of pituitary extract is contraindicated just as much as thyroid extract is in the treatment of Graves's disease. Beyond this, treatment must be directed to the relief of symptoms as they arise. The opposite condition of adiposogenital dystrophy, which develops as the result of atrophy or destruction of the pituitary gland, is a rare but very interesting disease. Loss of function of the pituitary gland may be due to a primary atrophy comparable to the atrophy of the thyroid gland in myxoedema, or it may be due to secondary changes following a period of hypersecretion. A similar sequence of events takes place in the thyroid gland when Graves's disease is followed by myxoedema. When the pituitary secretion fails early in life growth is arrested, the bones are not fully developed, the external genital organs remain undeveloped, the secondary sexual characters do not appear at puberty, and the skin is soft and smooth. These defects are chiefly due to loss of function of the anterior lobe. In consequence of failure of the posterior lobe sugar tolerance is raised and the subcutaneous fat is largely increased. In the adult this development of obesity is a striking feature. The fat chiefly accumulates in the supraclavicular fossae, in the lower part of the front and sides of the abdomen, at the back of the arms, over the hips, and upper part of the thighs. The face, hands, arms, legs, and feet usually are little if at all affected. The distribution of fat thus resembles that seen in adiposis dolorosa, but it is painless. The sugar tolerance is increased so that in some cases as much as 400 grains of glucose, if the stomach will retain

it, may be taken without producing any glycosuria. The temperature tends to be subnormal and the pulse to be slow and of low tension. The metabolic rate was frequently found by Plummer to be as much as 25 per cent. below normal. The sexual power is diminished and there may be impotence in the male and sterility in the female, with atrophic changes in the external genital organs. The skin is soft, cool, and smooth. Polyuria occurs in some cases and so diabetes insipidus has been attributed to a deficiency of the posterior lobe, but recent investigations by Houssay and Leschke indicate that this malady is due to a lesion of the tuber cinereum rather than of the hypophysis itself. It is, however, to be remembered that the hypodermic injection of 1 c.cm. pituitrin every day or two often controls the polyuria for the time being, as a single dose has reduced the amount of urine passed in twenty-four hours from 13,000 c.cm. to 1,800 c.cm. the next day. It was naturally hoped that pituitary extract would be able to supply the missing hormones and remove the symptoms in these cases just as thyroid extract does so promptly in myxoedema. Some improvement does follow the administration of two or three grains of the whole dried gland several times a day. Cushing has found 12 grains three times a day necessary in one case to produce an improvement. The results have so far been disappointing, and clearly indicate that we are still unable either by oral or subcutaneous administration of pituitary extract to make good the loss of the special hormones secreted by this gland. Apart from these cases pituitrin has proved to be of service in raising blood pressure in cases of shock or heart failure and in stimulating peristalsis in inertia of the bowel. In obstetric practice also, as a uterine stimulant it is a powerful though sometimes dangerous therapeutic agent. It may be given subcutaneously in doses of 10 to 30 minims, or in the treatment of shock it may be added to an intravenous saline injection.

SUPRARENAL GLAND.

The normal suprarenal gland cannot be detected by physical methods of examination or by x-ray examination, and only tumours of these glands may be large enough to be palpable during life. Disease of the gland can therefore only be detected by a consideration of the symptoms which occur when the normal functions are changed by alterations in their structure or functional activity. The cortex and medulla have different functions. The medulla produces adrenalin, which has been shown by Langley and Elliott to be a powerful stimulant of the sympathetic system. The cortex is probably concerned with the development of the genital system. These glands, like those we have already considered, may undergo changes which lead either to excessive activity, on the one hand, or to loss of function on the other. We know very little of the results of overaction of the chromaffin tissue of the medulla with excess of adrenalin in the blood, though it has been suggested that it may be a factor in the production of the high blood pressure associated with granular kidney and other conditions. The overactivity of the suprarenal cortex which occurs in certain cases of hypernephroma in early life leads to a rare and interesting condition of precocious sexual development associated with somnolence. Destructive lesions of the suprarenal glands, most commonly due to tuberculous infection, cause the symptoms of Addison's disease, which are characteristic in the fully developed malady, but difficult to recognize in its incipient stages. The progressive asthenia, gradual fall of blood pressure, and pigmentation of the skin, and especially of the mucous membrane of the mouth, are the most helpful early signs of suprarenal failure. The treatment of suprarenal insufficiency is unsatisfactory, as we cannot as yet replace the lost function by the use of suprarenal extract in any known form, administered either by ingestion or injection, and I have not seen any definite improvement following this treatment in Addison's disease. Cases of recovery have been recorded, but it is possible that the symptoms have been due to loss of one suprarenal gland and have disappeared owing to compensation by the other gland. In a recently recorded case of recovery it was ultimately found that the symptoms had been due to a destructive lesion of one suprarenal gland. The value of adrenalin as a therapeutic agent is so well known that it is only necessary to mention its powerful local action in

arresting haemorrhage from the skin and mucous membrane by causing constriction of the blood vessels, and its useful action in stimulating the heart and raising blood pressure when given intravenously in shock or in the collapse of toxic conditions. Liq. adrenalini hydrochlor. may be given subcutaneously in doses from $\text{m} \frac{1}{2}$ up to $\text{m} \times$ for the relief of spasmodic asthma with marked benefit. Professor J. N. Langley has found that adrenalin also relaxes the oesophagus, and suggested to me several years ago that it would be well to try it in cases of spasmodic stricture. In adopting this suggestion the adrenalin has been given by the mouth, in the hope that its local action on the oesophagus would relax the spasm, so as to avoid the frequent repetition of hypodermic injections. In two recent cases of oesophageal spasm under my care at the Manchester Royal Infirmary the administration of $\text{m} \times \text{v}$ of adrenalin solution in half an ounce of water five or ten minutes before each meal has had a striking effect in relaxing or preventing the spasm, so that the patients were able to take their food without difficulty.

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A FATAL CASE OF MALIGNANT TERTIAN MALARIA CONTRACTED IN THE NORTH OF ENGLAND.

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The following preliminary note of a fatal case of malignant tertian malaria contracted in the North of England is recorded:

M. B., a girl typist, aged 18, a resident in Liverpool, was admitted in a moribund condition to the Royal Infirmary, Liverpool, at 4.30 p.m., October 12th, 1920, under the care of Dr. J. C. Matthews. The only history obtainable at the time was the following: The patient had been seriously ill for a few days; on account of delirium her doctors thought she might have meningitis. After a slight haemorrhage, apparently from the vagina, she was also seen by a gynaecologist, who diagnosed metrorrhagia, and, finding her profoundly anaemic and unconscious, sent her to hospital.

On admission the patient, a poorly developed girl, was in *extremis*, unconscious, blanched but not jaundiced, and pulseless. The temperature was 102.6°. There was no evidence of meningitis, nor of the exanthemata. She died two hours later.

The *post-mortem* examination was made twenty hours after death. Blood anaemic. Brain: apparently normal, no meningitis. Lungs: a moderate amount of oedema and muco-purulent bronchitis. Heart: weight 8 oz., normal, no fatty degeneration. Mouth: healthy, no trace of pyorrhoea. Oesophagus, stomach, and intestines opened from end to end—normal, no evidence of blood. Some of the lumbar lymphatic glands slightly enlarged, and red like haemolymph glands. Liver: weight 3 lb., slightly browner than normal, no haemosiderin reaction. Spleen: 1 lb. 7 oz., retains its shape, of normal consistency, but dark, rather like malaria. Pancreas, suprarenals, kidneys and bladder normal. Uterus: normal size, but menstruating; one haemorrhagic corpus luteum. Bone marrow of the shaft of the femur a uniform terra-cotta red,* that of the sternum redder and more succulent than normal.

The salient features of the *post-mortem* examination were therefore the anaemia, the greatly enlarged spleen, and the marked erythroblastic reaction of the bone marrow. The patient's friends, who had very reluctantly granted the necropsy, demanded the death certificate before it was finished so as to obtain an order for burial before the registrar's office closed. A provisional diagnosis was therefore considered. There was no evidence of leucocythaemia—the spleen in particular was too small for the

* The colour closely resembled that shown by Carnegie Dickson in the transverse section of the bone marrow of the femur from a case of pernicious anaemia (Plate XI, Fig. 2). It was not so dark as the marrow from a case of acute streptococcal septicaemia (Plate XI, Fig. 1, W. E. C. Dickson, *The Bone Marrow*, Longmans Green and Co., London, 1908).