borderland manifestations. But another lesson is to be derived from this case: the borderland symptoms were referred to a doctor, who was consulted again and again, but who jumped at conclusions that because of the patient's habits he had contracted a cough which he said was "a reflex from his liver." He omitted to auscultate his chest, to ask to see the sputum, or to inquire into the progress of events so far as they concerned the general nutrition of the sick man. More mistakes, as we all know, are made from lack of painstaking than from want of knowledge, and this case is a regrettable example of mischief that might have been curtailed by being earlier discovered had this scrap of common knowledge been borne in mind.

(To be continued.)

OUR PRESENT KNOWLEDGE OF THE THYROID GLAND;

WITH A PRELIMINARY REPORT ON A CASE OF
THYROID GRAFTING.

By MARCUS MAMOURIAN, F.R.C.S.E.,

ASSISTANT SURGEON, THE DISTRICT INFIRMARY AND CHILDREN'S
HOSPITAL, ASHTON-UNDER-LYNE.

THE work that has been done on the thyroid gland within recent years has acquired enormous dimensions, but, remarkably enough, the clinical, operative, and pathological observations and physiological investigations constitute a perfectly congruous study of wide practical applicability and interest which concerns almost every branch of medical science.

In a comprehensive survey of this subject it is of advantage to refer, first of all, to a few developmental points.

1. Development.

The thyroid gland is said to have a double origin. The main portion arises from the base of the tongue and grows downwards into the neck, where it bifurcates. This pharyngeal bud or projection is, to begin with, a tube—which suggests the probability of the secretion being poured into the mouth in antenatal life—and is known as the thyroglossal duct. Out of the bifurcated end are formed the isthmus and the larger portions of the lobes, the lesser segments of which were thought to originate from the fourth branchial arches, but this view of an "epiblastic contribution" is not now generally accepted. In course of time the hyoid bone is developed across the duct, which thus becomes divided into a lingual and a thyroid section and ultimately obliterated, the meatus of the lingual portion remaining as the familiar foramen caecum, and the thyroid part occasionally surviving as the so-called pyramidal lobe. In some instances a mass or masses of thyroid substance fail to coalesce with the main gland, and are known as "accessory thyroids." Our study of the development of the thyroid not only throws light upon the anatomical peculiarities already indicated, but it also explains certain pathological conditions which are met with in the neck, such as the vascular tumour which grows at the base of the tongue (lingual thyroid) and the cysts in the middle line of the neck, both being thyroglossal in origin, and which are liable to be mistaken for the cystic enlargements of the hyoid bursae and dermoids, but the latter are rarely situated mesially, as they are attached, as a rule, to the great cornu of the hyoid, the styloid, or the mastoid processes.

2. Anatomy.

The important fact to bear in mind is that the gland is tied down to the trachea by cervical fascia (the surgical capsule); hence the liability of the windpipe to compressional changes and the diagnostic importance of the act of swallowing. With the exception of giant goitres, which, owing to their size, impede tracheal movements, fixation here, as in the breast, is indicative of malignancy, and more definitely so if there be aphonia. The inferior thyroid arteries are of primary surgical importance owing to their intimate relationship with the recurrent laryngeal nerves, which are liable to be torn or included in the ligatures for these vessels.

* Delivered to the Twenty Club, March, 1914.

Physiology.

The physiology of the thyroid gland is a chapter of absorbing interest. It presents for consideration functions of the most intricate order by means of an internal secretion, which has eluded the efforts of many investigators to analyse or identify it definitely. We are all familiar with the microscopical appearances of a section of the gland—the spheroid vesicles lined with columnar epithelium and filled with colloid material. A noteworthy feature is that, with the exception of the colloid substance, the gland shows no other sign of secretory activity, and no secretion or its active ingredients have been isolated or their presence proved in the veins or the efferent lymphatics of the gland. For all that, there can be no doubt of the great rôle that the thyroid plays in animal economy, and Dreschel's opinion to the effect "that it secretes a complex material which subserves more than one essential function" is doubtless correct and conforms to the present conception of glandular secretions in general, which are looked upon as influencing metabolism by acting as excitants or stimuli (hormones) to some or as agents of control or inhibition to other organs. It is now conclusively proved that the thyroid has a profound influence on the metabolism of growth, specially with regard to calcium and nervous tissues; that it affects sexual functions, as evidenced by its increased activity during menstruation, pregnancy, and lactation and the retrogressive changes observed in the genitalia in experimental thyroid inefficiency; that it is concerned in the glycogenic work of the liver by its inhibitory action upon the pancreas, the pancreatic hormone being the principal stimulus to the sugar-producing cells of the liver; further, it influences the circulation by virtue of its vaso-dilator property, and the fact that the gland receives part of its blood supply from two cerebral vessels (the vertebrals) points to the probability of its having a bearing on intracranial blood pressure. There is also what Gley terms its neurochemical relationship with the other ductless glands, the parathyroids, the pituitary, the suprarenals, the ovaries, and the thymus, which is pretty constantly in a condition of hyperplasia in cases of Graves's disease.

Such substances as have been chemically obtained have not shown the potency of the gland extract, and of which may be mentioned Bubnow's thyro-protein, which acts in the manner of an enzyme; Fraenkel's thyro-antitoxin—a significant term suggestive of the view, now held by many workers, that the thyroid secretion possesses the property of neutralizing toxins, and that in Graves's disease this defensive element is absent or impaired; Roos and Bauman's thyro-iodine, which also contains a trace of phosphorus. In Hutchinson's opinion the iodine and phosphorus containing substance is the active one.

3. Pharmacology and Therapeutics of the Gland Extract.

Allusion has already been made to the vaso-dilator effect of the gland's secretion. Accordingly, the extract lowers the blood pressure. It produces tachycardia, diuresis, and its prolonged administration brings on glycosuria. It causes a mononuclear leucocytosis (a condition present in Graves's disease, and which becomes reduced after the ligation of the vessels or hemisection of the gland). No true exophthalmos has ever been produced.

Thyroid medication may be said to occupy the foremost place in organotherapy. The brilliant results obtained by the exhibition of this drug in myxoedema are well known. In some rare instances, however, it fails to act, and then the question of other measures arises. In this connexion the following notes on a case of congenital myxoedema may be of interest: "E. H., 4 years of age, a typical cretin (Fig. 1), was brought to the Ashton Infirmary early in 1907. For about three years he was treated with thyroid extract without intermission. He came under my care in January, 1910, and I continued the treatment for over six months, prescribing 20 grains of the dry extract per day. Neither his physical nor mental condition underwent any appreciable change. I then decided to try grafting. I had a sheep killed in hospital while the patient was being anaesthetized. I removed the thyroid, placed it in hot saline, and after incising it in several places planted it into the child's omentum, which I scarified with a needle.

Now this case has made wonderful headway, as shown in the photograph (Fig. 2) recently taken (four years after operation). The boy has entirely lost his repulsive countenance, and looks pleasant and intelligent. He

Fig. 1.

can now read and write, tell the time, and recognize coinage. I have had excellent reports of him from his teacher. He has grown to the extent of 10 inches in four years. Since the operation he has very occasionally had a 5-grain tablet owing to a stutter which he develops at times, and which, according to the observation of the boy's mother, completely disappears when a small dose of the extract is given. Thyroid grafting has been carried out by many surgeons, notably by Bircher, Horsley, Payer, the Mayos, and others, the favourite sites being the subcutaneous tissue,

the spleen, and recently Kocher has advocated the medullary cavity of the tibia. No one, however, so far as I know, has hitherto utilized the omentum, which by virtue of its vascularity strikes me as eminently suited for all kinds of grafts, be they thyroid or ovarian.

In parenchymatous goitres, especially those associated with myxoedema, there is no better treatment than thyroid extract. No case should be submitted to operation without a trial of this remedy in preference to iodine and iodides, which bring about local adhesions and render the work of the surgeon more difficult. Thyroid extract is a potent remedy in cases of nocturnal incontinence in children, in obesity; but in the latter condition its use is not free from risk, as, in addition to its depressing effects upon the circulation, it may cause wastage of albuminous substances. It has been recommended in the treatment of rheumatoid arthritis, spasmodic torticollis, and adenoids. It has been used successfully in recurrent mammary cancer. Could it be, one is tempted to ask, by inducing over-production of pancreatic enzymes which Beard regards as the only scientific cure of malignant disease? I am convinced that in many cases of cancer large doses of thyroid have an inhibitory influence upon the growth. The extract has a field of usefulness in cardio-renal conditions with high arterial tension, especially when the nitrite group of drugs has proved of no avail. It has been used in dermatology in conditions characterized by keratosis and in post-operative tetany (but the parathyroid extract is to be preferred). It is one of the most useful drugs in gynaecological conditions, notably menstrual derangements, and as a preventive of an early menopause. Its employment in Graves's disease has proved worse than useless.

can now read and write, tell the time, and recognize coinage. I have had excellent reports of him from his teacher. He has grown to the extent of 10 inches in four years. Since the operation he has very occasionally had a 5-grain tablet owing to a stutter which he develops at times, and which, according to the observation of the boy's mother, completely disappears when a small dose of the extract is given. Thyroid grafting has been carried out by many surgeons, notably by Bircher, Horsley, Payer, the Mayos, and others, the favourite sites being the subcutaneous tissue,

4. Pathology and Treatment.

Myxoedema.—Reference has already been made to this condition, which results from congenital absence, atrophy or parenchymatous degeneration of the gland. Three types are recognized—(a) the infantile, with its interesting geographical distribution, (b) the adult (Gull's disease), and (c) the post-operative. There is no difficulty, as a rule, in recognizing a typical cretin with the stunted body, bloated face, flat nose, puffy eyelids, the scanty hair, and the striking mental sluggishness. In Gull's disease the changes are more or less similar, but the localized distribution of the oedema, as in the hands, the neck, etc., might be mistaken for diffuse lipomatosis. It may be pointed out that the tumefaction of the subcutaneous tissue is not a true oedema but a hyperplasia of connective tissue rich in mucin and therefore embryonic in type.

Thyroiditis.—The thyroid is seldom attacked by inflammatory conditions, but may become secondarily infected in the course of certain fevers, specially in pneumonia and typhoid.

Malignant Disease (rarely met with).—The gland may be the seat of either carcinoma or sarcoma. Sometimes the metastases of definite thyroid gland cancers consist of normal thyroid tissue by way of atavism (De Quervain). The metastatic growths show a selective preference for the osseous system.

Goitre.—This term is applied generally to enlarged thyroids, but enlargement may be brought about by a variety of structural changes; thus we have the parenchymatous (cystic or colloid), the fibrous adenomatous, and the vascular—terms which are descriptions in themselves. There is no correlation between the dimensions that the gland may attain and the constitutional effects produced. Thus, we may have goitre and myxoedema, goitre and Graves's disease, and Graves's disease or myxoedema without goitre.

Puzzling as these differences may appear, they are easily understood by the aid of the microscope, and the work of Wilson and McArty of the Mayo clinic has helped in explaining these seeming anomalies of thyroid pathology. As a rule each lobe is visibly hypertrophied. Sometimes the isthmus is the prominent part. One is liable to be misled however, by retrotracheal, retroclavicular and retrosternal enlargements; the latter have been mistaken for

Fig. 3.

mediastinal tumours. Osler and Packard have reported a case of a cystic accessory thyroid filling the entire right pleura. Pressure effects are not always dependent upon size. The firm fibrous goitre may reduce the tracheal lumen to a mere chink. In cases of intractable asthma or paroxysmal dyspnoea it is worth while to bear this in mind.

The sudden development of a thyroid tumour points to haemorrhage in the gland substance. A parenchymatous

Fig. 2.

goitre may acquire enormous dimensions which may produce marked congestion of the veins of the face, chest and upper extremities, and which may lead to actual thrombosis. If a goitre is producing respiratory embarrassment, the sooner operation is undertaken the better.

Graves's Disease.—The cardinal signs of exophthalmos, tachycardia, and tremor make the diagnosis of this condition easy. The ocular signs are well known. The etiology of the disease is obscure. The main issues are (a) that it is a neurosis, (b) that it is the result of perverted secretion or hypersecretion, (c) that it is due to sepsis. Pathologists have described haemorrhages in the fourth ventricle. If these haemorrhages were a constant feature we may be justified in assuming that the glycosuria of Graves resulted from a medullary lesion analogous to Claude Bernard's puncture of the fourth ventricle. Amongst the noteworthy features of this condition we have the cutaneous manifestations, which may take the form of pruritus, leucoderma, or of a pigmentation akin to that of Addison's disease; the unsusceptibility of these patients to cold, the occurrence of oedema, both simple and angioneurotic, and of intractable vomiting and diarrhoea. Singularly enough, in the glycosuria of Graves, as in diabetes, the patellar reflexes are lost.

The relation of hyperthyroid states to tuberculosis has been studied by Professor G. R. Murray, who holds the view that there is some sort of antagonism between the two conditions, as these patients rarely die from tuberculosis, and even if a focus be present it remains quiescent as long as the hyperthyroidism continues. The case which he mentioned in his presidential address at Brighton was operated on by me. There can be no doubt that, after the removal of the major portion of the gland, the patient, who had had the disease for over twelve years, succumbed to acute phthisis.

The treatment of Graves's disease still remains on an unsatisfactory basis. The bulk of the cases are still being treated with bromides and iodides. Kocher thinks well of phosphorus, and the Mayos and Thurstan Holland of *x* rays. The late A. Gibson claimed to have cured most of his cases by suprarenal gland extract, but the experience of others is very disappointing. Moebius's serum has not been a success. Pechlau recently reported a case which was cured by the administration of the milk of a thyroidectomized woman. Sir Thomas Fraser used to speak of marriage as having a curative influence on adolescent female exophthalmics. Good results have been obtained by antiseptic medication of the bowel and the elimination of all sources of sepsis. The excision or short-circuiting of the colon is not a measure likely to meet with general acceptance.

Surgery can claim the most brilliant and the most lasting results, but in this connexion we must bear in mind that institutional life, *x*-ray exposures, and tonic medication contribute to no small extent to the recovery of these patients. Crile's anoci-association method has a useful field in this condition in which "psychic strain" is a pronounced characteristic. Kocher favours the plan of ligating the vessels at successive sittings. Most surgeons prefer the removal of one lobe with the isthmus. One or both vessels of the remaining lobe may be ligatured later if the improvement after hemithyroidectomy is not satisfactory. Halsted has recommended the excision of practically the whole gland, leaving merely a strip on each side to maintain the blood supply to the parathyroids.

I have noticed that exophthalmic subjects, thin or even emaciated as they are as a rule, put on fat to an extraordinary extent after operation (Fig. 3). I have never seen complete recession of the eyes after operation or other treatment. Drs. Bythell and Barclay of Manchester assure me that they have obtained complete disappearance of exophthalmos by *x*-ray treatment alone.

THE *Journal of the American Medical Association* lately called attention to a two year graduate course offered by the University of Minnesota for the training of doctors who desire to specialize in ophthalmology. This course is analogous to the graduate courses offered by several medical schools for the training of health officers. It is thought probable that similar courses will be established for the training of those who wish to limit their practice to other special provinces of medicine.

NICOLLE AND BLAIZOT'S VACCINE IN THE TREATMENT OF GONORRHOEA.

BY

R. DONALDSON, M.A., M.B., CH.B., F.R.C.S.E., D.P.H.,
PATHOLOGIST, ROYAL BERKS HOSPITAL, READING.

THIS vaccine, which goes by the name of "Dimegon," was prepared by MM. Ch. Nicolle and L. Blaizot, of the Pasteur Institute, Tunis, and placed on the market as a stable, non-toxic vaccine for use in all cases of gonorrhoea. In October, 1913,¹ they maintained its superiority over the vaccines in ordinary use.

The drawbacks to the use of the latter, and of gonococcal vaccines in particular, where results have been far from uniform or encouraging, had led them to seek a means of overcoming these defects. In their opinion the two chief obstacles to the success of vaccine-therapy are the present crude methods of sterilizing the living cultures, and the more or less constant toxicity of all vaccines, but more especially of gonococcal vaccines. Even Besredka's method of sensitizing has failed, according to them, to abolish this toxicity.

They stated that, as the result of a year and a half's work, they had succeeded in entirely suppressing the toxicity of gonococcal vaccines, and claimed by their new method of sterilizing to have prepared a vaccine in which the organismal elements are conserved practically in the same condition as obtains in the living culture—in other words, that their vaccine was non-toxic and stable. How this was attained was not at first divulged; the authors merely stated that the toxicity had been abolished by growing the organisms on a special medium, while stability had been achieved by the use of a special solution as lethal vehicle.

Their personal statistics up to that time covered some 200 cases, including 24 cases of ophthalmia, 3 of rheumatism, 25 of orchitis, and 127 cases of acute and chronic urethritis. They stated that ophthalmia was cured after a few injections, sometimes after one, an injection being given each day; that in acute orchitis the pain disappeared in a few hours, or at most within a day or two after the first injection, fever declined, and the patient was able almost at once to resume his daily occupation; and that gonorrhoeal rheumatism rapidly cleared up under two to eight injections. The most striking case was one where a woman, bed-ridden for eight months, was able to come for the eighth injection. In acute urethritis the symptoms, they stated, cleared up with equal rapidity. The discharge ceased later, but in many cases it had disappeared after the third injection. They recommended that the injections, which were repeated every two days, should be continued till seven or eight had been given. Simultaneous local treatment had a favourable effect. None of the acute cases under prompt treatment developed any extra-urethral complications. Old-standing gleet (a year and a half) had been cured by this vaccine, the injections being given every three or four days.

Truly these are wonderful results and all obtained without provoking any untoward or disagreeable reaction! Beyond these facts, however, nothing was known about this vaccine till in November, 1913, Nicolle and Blaizot² revealed their secret.

Vaccines prepared in the usual way are damaged by the coagulating effect of heat, and are unstable because they undergo later a process of autolysis. To obviate these disadvantages the authors make use of a fluoride solution since fluorides have been shown by other workers not to possess the property of coagulating albumin.

Method of Preparation.

The organisms are suspended in a 0.7 per cent. solution of sodium fluoride in which they die after a variable time depending on the temperature and species. For instance, gonococci die after forty-eight hours' exposure in an ice-chest to the action of the fluoride. The authors claim that the organisms remain practically unaltered and, since the solution retards autolysis, long preserve their morphological and staining characters. The fluoride is also said to aid in diminishing the toxicity. The latter, however, is mainly brought about by growing the gonococci on special culture media which at first consisted of: Broth 100, urea 0.4, glucose 2, phosphate of ammonia 0.5, agar 1.5.

To this in tubes of 5 c.cm. each are added 0.5 c.cm. rabbit serum. The gonococcus is first grown on this and, by sub-