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EXOPHTHALMIC GOITRE,

by

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## I N T R O D U C T I O N .

giving scope of

### THE THESIS.

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In the whole realm of Medicine, perhaps there is no subject which has attracted so much patient investigation, laborious research and clinical acumen as Exophthalmic Goitre.

The problem of cause and cure is one which commends itself to the Clinician, Pathologist, Physician and Surgeon alike and for these reasons:-

- I. To save the human subject the distress of grievous symptoms which cripple so many at the fastigium of functional activity.
- II. The disease is a very definite clinical entity.
- III. The wonderful result in the treatment and cure of Myxoedema leads one on to the hope that the cause of Exophthalmic goitre may be found and corrected as simply.

"Obstacles are given to be overcome" and the results of labour and expense of research in this field has led to a great increase in the knowledge of the use, the work and of the necessity of the ductless glands and their internal secretion. One result of the research has been to show the profound/

profound effect of the internal secretions, the dependence of one ductless gland upon another so little by little this vast unknown field is being surveyed.

The problem is complicated by the fact that the secretions of the ductless glands are both co-related and interdependent so the investigation of all of them must go together.

My attention has been particularly drawn to this disease because my wife, a young woman of 30, suffered from the distressing symptoms associated with Exophthalmic Goitre. I was impressed by the unsatisfactory state of our knowledge of the cause and treatment - how little is known about the action and secretion of the whole Thyroid apparatus - how many hypotheses have been propounded to explain the peculiar symptoms of this disease. The cause has been ascribed to an altered condition of the blood, to an affection of the sympathetic, to a degeneration of the emotional nervous system, to a disorder of the nuclei about the IVth Ventricle, to a diseased condition of the Thyroid itself, to changes in the Adrenals with derangement of its internal secretion which acts in a harmful manner on the Thyroid to an auto-intoxication from the alimentary tract.

There/

There are so many methods of treatment and so many specifics quoted, in conversation with medical men so many have guaranteed to cure the case, yet when these were tried on my wife and other patients the results guaranteed were looked for in vain. Rest, absolute rest, mental as well as physical is the best method of cure with good hygienic conditions. But in general practice, how often this problem comes up, how to get this physiological rest, when the patient, as so many do, belongs to the lower walks of life. It is impossible in many cases, for consider our present conditions of housing in the coal mining districts, the anxiety to run a house on a definite income which is small for the provision of all the needs of a growing family, the necessity for the patient to work in order to keep her house a home or to get her own living. As Emeritus Professor John Chiene used to tell us in my student days, "It is no good ordering a clerk belonging to a mercantile house to go for a trip to the Mediterranean in order to cure writer's cramp".

The writer last year went over to the United States after visiting London and his own Alma Mater to see if any fresh light could be thrown upon the cause and cure of this disease and much which follows is the embodiment of what has been gained from reading, advice and help given from various medical men some of whom have more than an international reputation.

In America and especially in the surgical world, there is a tendency to draw up a new classification of the diseases of the Thyroid:-

- i. Simple - including all forms of enlargement which are not harmful.
- ii. Malignant - due to neoplasms
- iii. Toxic - including Exophthalmic Goitre and cases where an enlargement of the Thyroid which has been present for many years, shows definite symptoms of hyperthyroidism.

The object of this thesis is to present a concise summary of recent research upon the Thyroid gland in so far as it applies to Exophthalmic Goitre and to see what data are available to explain the etiology and symptoms of the disease.

The great aim of the Science of Medicine is surely not to treat the symptoms of disease, thus giving relief to sufferers - important as this is - but the most important object is not to treat symptoms but to find out the cause and to attack the root.

So much of our present day medicine, especially in the work of a country practitioner, is to treat the symptoms and thus the sum total of human knowledge in things medical is not being increased as it should be.

Until recently the abnormality regarding the quality and excessive quantity of the Thyroid secretion was regarded as being the primary and essential factor in producing Exophthalmic Goitre.

But/

But recent investigations referred to, together with others which will be referred to later, have rendered this view somewhat doubtful. They seem to indicate rather that while it is one of the most important features of the disease, the Thyroid perversion is a manifestation only, a symptom and is the direct outcome of some other and **obscure** factors. Contrary to former belief, it has recently been shown that while a certain number of symptoms of Exophthalmic Goitre are due to Thyroid excess and can be produced experimentally by overfeeding with the gland, there are others which cannot be explained in this manner and for which some other causes must be found.

A great part of the mystery which surrounds this disease is due to the almost complete lack of epidemiological research regarding it.

It is proposed here to consider the disease historically, briefly refer to the anatomy of the gland - the pathology - give the clinical picture - put forward various features which lead to the diagnosis - give the treatment and conclude by giving a brief summary, laying stress upon the chief points.

#### HISTORY/

## H I S T O R Y .

There are no references in the classics of this disease and because there are so many and varied symptoms, also because the pathology is so obscure, the clinical picture has developed slowly.

MORGAGNI in the XVIIIth century refers to cases which are suggestive of this disease but these references are far from being clear.

The Italian FLAJANI in 1802 published a dissertation which was both meagre and inadequate, but the Italians because of this call the disease "morbo di Flajani". Professor LAYCOCK (vide infra) says of Flajani "he believed the Thyroid gland was the seat of the malady and that an acrid humour deposited there was the cause. Such being the case (I quote from Begbie's translation) the indication for cure must consist in effecting the dissolution of the deposited or stagnant humour. For this purpose cold compresses saturated with a solution of Sal ammoniac or vinegar and water were applied, after the application has been employed for twenty days there was a visible diminution of the tumour". It is interesting to note that at that early date, ice was applied to the tumour "with signal service".

To Dr. PARRY, a Bath physician, in 1825

we/

we owe the first contribution which is of any value. He gives notes of eight cases the first one observed in 1786 being typical, he describes the exophthalmos "the eyes were protruded from their sockets and the countenance exhibited an appearance of agitation and distress especially in any muscular movement". Having noted the proptosis, he described the symptomatic tripod of thyroid enlargement and palpitation of the heart. Dr. PARRY was struck by the nervous symptoms also he had "the notion of some connection between the malady of the heart and the bronchocele".

In Germany in 1828, ADELMANN reported two cases with the post mortem finding of one case.

GRAVES, a famous Irish physician in 1835 made an important report. He did not make the mistake of PARRY, but realized that the goitre was not the same as in the endemic disease, however, he did not go any further than PARRY in the interpretation of his cases. Like PARRY he notices the nervous symptoms and he looked upon the heart as the cause. It was after publishing his textbook in 1843 that his name was associated with the disease, though, if any name should be given to this disease it ought to be PARRY'S.

VON BASEDOW in 1840 published a fuller description and a more complete analysis of four cases - in the spirit of humeral pathology he looked at the/

the disease as a result of a dyscrasia, though later he added anaemia to the dyscrasia. He, like PARRY, noted the "Rheumatism" in the patient's previous history, he also drew attention to the important symptoms, feeling of warmth, nervousness, restlessness, rapidity of breathing, profuse perspiration and headache. He also noted the improvement in pregnancy. When explaining the cause of the exophthalmos, he stated it was due to "a strenuous hypertrophy of the tissues behind the bulb."

Dr. J. BEGBIE, on January 3rd, 1849, read an original communication before the Medico-Chirurgical Society of Edinburgh on "Anaemia and its consequences - Enlargement of the Thyroid Gland and Eyeballs. Anaemia and Goitre are they related"? He considered that Anaemia was the cause and advised the "full use of iron" to improve the blood, change of air, travelling, passive exercises also do good". Persistence is absolutely necessary, both on the part of patient and his attendant.

Dr. WARBURTON BEGBIE (vide infra) in speaking of this paper says:- "in 1839 this disease was carefully observed by Dr. J. BEGBIE and in course of the succeeding ten years again and again recognised - till in the form of a memoir, his observations, comprehending a theory as to its origin, the proof of its amenability to treatment and important suggestions as to the means employed, was brought before this Society/

Society in 1849.

STOKES in 1854 gathered together and enlarged upon the findings of FLAJANI, PARRY and GRAVES, described accurately the vascular phenomena. In discussing the cause, he held to a cardiac theory, he says:- "there are strong reasons for holding that the disease is originally a neurosis of the heart, and perhaps, also of the cervical vessels themselves". He said the proptosis was due to an increase of the vitreous and aqueous humour.

KOEBEN, 1855, published some cases, and in his opinion a lesion of the sympathetic nerves was the etiological factor, and this theory held the popular fancy for some time, as it was aided by the celebrated experiments of CLAUDE BERNARD.

TROUSSEAU, in 1860, who had seen a case some 16 or 17 years before, suggested the name of the disease should be called after the name of Dr. Graves. However, in 1858, A. HIRSCH advocated the name BASEDOW'S disease and both FISCHER and CHARCOT in 1859 use this name. The French use terms cachexia exophthalmique, or goitre exophthalmique, and the latter term is the more prevalent in their medical journals.

In 1862 CHARCOT discovered the importance of the tremor. In 1860 CHARCOT and TROUSSEAU described/

described the incomplete form of the disease "formes frustes".

In 1863, two great men of the Edinburgh Medical School read original articles before the Medico-Chirurgical Society in Edinburgh.

Dr. LAYCOCK, Professor of Medicine on Jan. 7, and June 3rd, said the cause of the disease is complex. "I do not, however, think that a theory founded on the innervation only, would be satisfactory. The Thyroid is a part of a system of tissues to which the Thymus and Suprarenals belong, and all of which have important developmental, if not functional relations with the genetic glands. So that a satisfactory theory should include the relations of the Thymus, Thyroid and the capsules to the ovaria and Testes and of each of the nerve centres". He quotes the late Mr. Aran, "who endeavouring to explain the etiology of exophthalmos, associated with bronchocele and cardiac, as well as vascular disturbance, had made full use of the important experiments of M. CLAUDE BERNARD, very specially attaching importance to the influence exerted by the sympathetic or the orbital muscle of H. MULLER, the action of which is to carry the eyeball forward". The name of this paper "The cause and nature of the vascular kind of Bronchocele and of the Pulsations and Palpations termed Anaemic".

On/

On July 1st 1863, Dr. WARBURTON BEGBIE, a Physician of the Royal Infirmary, submitted his original article in which he said the cause of this disease was anaemia, also some morbid condition of the vaso-motor system. He said the exophthalmos was due to venous congestion. I think a more probable view is, that the protrusion of the eyes was due to pressure on the veins exerted by the muscles of the neck. He recorded intermittent albuminuria generally considerable and sometimes excessive, but this has not been proved to be a common feature of the disease.

TROUSSEAU rejected the anaemia theory and regards the anaemia as secondary to cardiac palpitations arterial pulsations and phenomena connected with both the eye and the thyroid gland. He considered "that the primary seat of the disease was a lesion of the grand sympathetic". He was the first to use Digitalis, also he applied cold compresses. He recorded pulmonary intestinal meningeal, and cerebral haemorrhages but these have not been found by others.

GROS in 1864 suggested the possibility of the participation of the Vagus and the vagus was combined with the sympathetic theory.

About this time MARIE fully investigated the symptom of tremor.

From 1864 to 1870 much work was done on the/

the Continent , DESMARIES, VON GRAEFE and STELLWAG, made more accurate study of the eye symptoms.

Also about this time CHVOSTEH senior studied the nervous and electrical conditions and found the resistance to the galvanic currents lessened, it is probably due to moisture and perhaps to atrophy of the skin.

In 1886, G. GAUTHIER put forth the suggestion that the Thyroid was the seat of the cause of the disease and MOEBIUS clearly stated this in the same year. MOEBIUS AND REHN worked at the anti-myxoedema theory.

Later MOEBIUS stated "BASEDOW'S disease is an intoxication due to the morbid function of the Thyroid gland". "If it is true that the toxic substances are formed in the body which are neutralized by the Thyroid secretion in the circulation or in the gland itself BASEDOW'S disease can be looked upon as a hyperthyroidisation".

"A priori, a normal thyroid, by relative excess due to a diminished amount of metabolic poisons to neutralise, may cause the symptoms of BASEDOW'S disease, but there are no facts to prove this. Everything points to a primary disease of the gland but in this case we must assume more than a hyperthyroidisation that causes not only too much but also a poor secretion".

MOEBIUS/

MOEBIUS admitted the probability of a congenital predisposition, also the influence of puberty, chlorosis, pregnancy, confinement and infective diseases as factors.

He asserted that the morbid product of the exophthalmic form of goitre, acts upon the heart and vessels, the central nervous system and the skin. He said the exophthalmos was due to a local alteration in the blood vessels and the effect of the poison like that of other poisons on the nervous system is a selective one.

In 1888 BERTOYE of Lyons, published the result of extensive investigations and found high temperature during long or short periods and of different degrees of severity, there is the subjective symptom of warmth or even heat, but actual fever is extremely rare.

The late Professor W. S. GREENFIELD, of Edinburgh, was the first in 1893 to draw attention to the distinct and certain specific alteration in the thyroid gland itself in exophthalmic goitre, i.e. a hyperplasia of parenchyma and stroma with disappearance of colloid, epithelial cells increased numerically, but growing in an atypical way. Also changes in the cervical ganglia of the sympathetic showing marked hyperaemia in the more superficial parts/

parts, active invasion of the tissue by leucocytes and degenerative changes in the ganglion cells. In the central nervous system, he notices minute haemorrhages around the IVth ventricle. The modern history of research done on exophthalmic goitre, if written, would occupy many books and is without the scope of this thesis. The work done by BRYOM BRAMWELL, HECTOR HACKENZIE, VICTOR HORSLEY, and many others, as well as McCARRISON on the thyroid in health and disease, KENDALL on the chemical composition of the thyroid secretion and the synthetic formation of the active principle which he has called "thyroxin", the work done on the Basal Metabolic rate, the researches on the Endocrine glands and Internal secretions, have opened up a vast field of thought and of experimentation, which has disproved many of the theories held in the past, and will lead to the discovery of the true cause and hence the cure of exophthalmic goitre.

ANATOMY/

A N A T O M Y

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In man the thyroid apparatus consists of the gland proper, a variable number of parathyroids, accessory thyroids, portions of thyroid tissue lying anywhere between the base of the tongue and the aorta. In exercise of its functions the thyroid apparatus is specially associated with certain other hormone producing organs, the generative organs, the liver, the pancreas, the adrenals, the pituitary, and the thymus.

The gland itself consists of two lateral lobes, the right is usually larger than the left. The upper poles stretch from the middle of the thyroid cartilage, the lower lobes reach almost to the line of the sternum, the lobes are in close apposition to the sides of the pharynx trachea and extend backwards to the oesophagus.

The two lobes are united by an isthmus which is about half an inch in breadth and lies in front of the trachea between the second and fourth ring. It is in the isthmus that degenerative changes are liable to begin.

The gland moves with deglutition, a point of diagnostic importance.

In/

In 40% of cases, there is a process of gland tissue, the pyramidal lobe, which extends from the upper border of the isthmus upwards in front of the cricoid and thyroid cartilages towards the hyoid bone. Sometimes it is represented by a band of fibrous tissue or a narrow muscle, the levator glandular thyroideae. The gland varies in size and weight with age, sex and general nutrition being relatively large in youth, in females ( it is  $\frac{1}{3}$  heavier in females) and in the well nourished. In women it increases temporarily with menstruation and pregnancy. It weighs on an average only one ounce.

The gland is covered with a dense capsule of areolar tissue, it is richly supplied with blood vessels and lymphatics, which with the nerves penetrate into and traverse its interior supported by a network of interstitial tissue.

#### BLOOD SUPPLY.

The thyroid is one of the most vascular organs in the body, it has been estimated that the whole of the blood of the body passes through the gland every hour; it receives five times as much blood/

blood as the kidneys and nearly as much blood passes through its arteries as through the internal carotid and the vertebrales.

There are two main arteries on each side, the superior thyroid from the external carotid and the inferior thyroid from the subclavian (via thyroid axis) these are sometimes supplemented by a third, the thyroidea ima a branch from the innominate. These vessels are remarkable for their relatively large size, for their tortuosity and their numerous ramifications and very free anastomoses between soft- infr. thyroid art. of same side. Less free across mid line. The arteries divide and sub-divide till each follicle is surrounded by a close network of sinus like capillaries with which the vesicular epithelium is in perfect contact.

The veins, three in number, superior, middle and inferior thyroid, are correspondingly large and numerous inter-communicating freely, these are especially prominent in exophthalmic goitre. The veins are valveless, and the superior and middle thyroids empty into the internal jugular whilst the inferior thyroids empty into the left innominate vein.

LYMPHATIC/

### LYMPHATIC SYSTEM.

The lymph system is free, lymph spaces lie outside the peri-vesicular capillaries; these perialveolar spaces join with interlobular vessels joining large trunks which anastomose with plexuses lying beneath the capsule of the gland. From these plexuses two main trunks convey the lymph which probably contains the internal secretion to the circulation by way of the superior and inferior cervical glands, a few descend in front of the trachea to the pre-tracheal lymph glands.

### NERVE SUPPLY.

The superior and inferior laryngeal nerves from the vagus and the Sympathetic from the Superior (Mc CARRISON) the middle and inferior (CUNNINGHAM) cervical ganglion supply the gland. The fibres are distributed to the muscle cells of the vessels and to the secreting epithelium. The secretory fibres reach the cells from the cervical sympathetic, so according to CANNON, the secretion of the gland is directly under the control of sympathetic impulses. As the result of experimental stimulation it is found that the secretion issues as promptly as in five to seven seconds.

In /

In a gland with such a profoundly and accelerating katabolic action, we should expect to find that the sympathetic supply carried the chief secretory nerves. That this is so was proved by CANNON who joined the central end of the phrenic to the peripheral end of the cervical sympathetic nerve on the one side of a cat, so that the gland was stimulated with every breath. This resulted in tachycardia, increased excitability, loose motions, exophthalmos on the side of the operation, a great increase in metabolism and in some cases an increased size of the adrenal glands.

#### DEVELOPMENT.

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The gland takes origin from a single median outgrowth from the pharyngeal floor. As soon as the bud grows its end expands whilst its stalk narrows to form the thyro-glossal duct. Very early in the embryo there is an elevation round the pharyngeal opening of the duct, this is the tuberculum impar, it migrates forwards and the duct backwards so a little later the duct opens in a furrow immediately caudal to the tuberculum. At about this stage the duct begins to/

to obliterate, this process proceeds slowly and is seldom quite complete, a vestige of the duct, the foramen coecum of the tongue, remaining in the adult. Whilst this is going on, growth and lateral expansion of the bud continue, it becomes bi-lobed and has a divided lumen, all the while it undergoes a continuous relative displacement caudalwards. Soon its lumen appears. At about the tenth week of development the formation of vesicles commences, but it is not completed until after birth. The development of a pyramidal lobe is due to the development of gland tissue from that part of the thyro-glossal duct which has a double lumen and the more or less complete fusion or separation of the mass thus formed. Accessory thyroid glands near the hyoid bone are the result of a similar process in connection with isolated remnants of the duct. Some masses become detached from the main mass and wander downwards with the heart, these become accessory thyroids and are in all respects identical with the gland itself. These accessory thyroids may give rise to aberrant goitres for example lingual and also retrosternal varieties.

The thyroid gland being a ventral out-growth from the pharynx, sometimes retains in the thyro-glossal duct a vestigial remain of its old connection/

connection with the alimentary tract and it is probably due to this primitive course of the secretion that it, in contra-distinction to all other hormones is so easily absorbed when given by the mouth.

MARNIE has shown that the thyroid apparatus from the earliest period of evolutionary history has been an essential part of the digestive tract.

GASKELL has proved that the gland is so intimately related to the genital organs as at one time probably to have formed an integral part of them. In its most highly developed form in the human subject, it still retains its fundamental function of profoundly influencing nutrition, growth and reproduction, and is itself profoundly influenced by disorders of the alimentary tract and genitalia.

Histology/

HISTOLOGY and PHYSIOLOGY.

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The thyroid gland consists of a framework of connective tissue enclosing numerous spherical vesicles which are lined with cubical epithelium. These vesicles vary in size, they are smaller in the glands of the new born or young, whilst in the adult, they are smaller towards the centre, larger towards the periphery. Sometimes it seems as if the vesicles had branches or several vesicles had intercommunications.

The cavities of the vesicles contain a peculiar viscid liquid called colloid and it is unique in the fact that it contains organically combined iodine. This colloid material forms more than half its bulk. When 'resting' the vesicles are distended with colloid and the epithelial cells are flattened, when the gland is actively secreting the cells are more cubical and even columnar, there is little colloid material in the vesicle. The colloid may be looked upon as a reserve of iodine for the body. The 'resting' stage can be produced by giving iodine or iodine containing foods. The discharge of colloid can be affected by a meat diet which is poor in iodine; this Dr. CHALMERS WATSON found in his experiments on feeding rats with various/

various foods. Conversely the phase of thyroïdal activity can be produced at will, by the administration of iodine. This fact is made use of in Cleveland and on the shores of the Great Lakes in the north of the United States of America, where the endemic variety of goitre is so prevalent that the Educational Authorities daily give the children attending the schools a dose of diluted iodine and thus have practically caused endemic goitre to disappear.

The protoplasm of these epithelial cells is retiform in structure and often contains granules of a fatty character, these vary and lie near the vesicular edge of the cell. It is now generally accepted that these special granules which are formed by the protoplasm, swell up and pass out of the cell body as drops and these drops constitute the contents of the vesicles.

The nuclei of the cells are spherical and show a fine chromatin network, they are placed either at the centre or at the base and may almost fill the flattened cell. Mytotic figures and recent division forms of nuclei are commonly seen in the gland of the newborn and the young.

There is an intervesicular parenchyma containing/

containing cells scattered through it or arranged in masses, some of these are lymphocytes, others are foetal rests from which foetal adenomata are said to arise. The fresh section of the gland, the colloid is quite fluid or only slightly gelatinous and it is in this form that it reaches the circulation.

It has been proved by SWALE VINCENT and SOLLY, that herbivora have less need of the thyroid gland than other mammals as carnivora. It may be because the diet is different, but BLAIR BELL feels sure it is also due in some measure to the variations in the structure and function or degrees of function seen in other endocrine glands. Generally speaking herbivora whose food contains a high proportion of iodine show a high iodine-content, carnivora whose food contains a very little iodine show a low iodine-content, whereas in omnivora the content is variable. The colloid material is elaborated by the cells and lies in the vesicles, it is probably an emergency ration which is not called upon in the daily routine of the body. But the cells also elaborate the specific hormone for daily needs, probably from substances supplied to them in the blood. This colloid material morphologically is a colloidal substance though chemically it is not, it is insoluble in water, alcohol, ether and dilute/

dilute acids. It swells in acetic acid and strong alkalies and is generally acidophile. It stains freely with all acid aniline dyes, most readily with eosin, usually uniformly. It is granular or perfectly homogeneous, it may show some so called vacuoles, these are thought by some to be artefacts by others to be albuminous material in the colloid.

There is a great change when the gland begins to actively secrete, the capillary vessels become fuller, in the colloid the so called vacuoles appear and it is absorbed naturally, the absorption is more rapid at the periphery. The epithelial cells of the vesicles heighten, tending to become columnar. The protoplasm is granular and on the discharge of these granules in the form of a thin secretion into the vesicle, or directly into the lymph spaces, it may appear pale and full of vacuoles. The nucleus is placed centrally and does not fill the cell, the edge of the epithelium becomes irregular, merging into the colloid material. There is no increase in the stroma, but the intervesicular tissue may appear relatively increased, owing to the emptying of the vesicles of the colloid material.

The emergency ration is called upon when the supply of iodine in the food runs short, under the/

the demands of excessive sympathetic excitation, such as occur in rage or fright, at certain periods of life, such as puberty, menstruation, pregnancy, or lactation, and when the body is invaded by micro-organisms or subject to certain intoxications.

Iodine is present in many other organs of the body, but it exists in greater quantities in the thyroid, where the minimum necessary for health is 0.01% while the maximum 1.16% had been recovered, under normal conditions the diet always contains sufficient iodine for the upkeep of the minimal amount. The thyroid tissue is the only tissue which has the power to fix iodine in organic combination, the iodine exists in organic combination with the amidoacid group and is present in the proportion of .3 to .9 per cent per gramme of dried gland and the entire adult gland contains from 2 to 9 mgs. In exophthalmic goitre, there is a reduction, so that is less than normal and the thyroid may even be practically iodine free. There is a variation in the iodine content with age and diet, also season and sex, female animals have more thyroid tissue and more iodine therein per unit of body weight than males. The thyroid's state of activity is largely dependent upon the iodine available for the elaboration of the secretion.

The iodine in the colloid material exists in combination with a non-protein nitrogenous base

KENDALL of the Mayo Clinic in 1916 isolated a pure crystalline substance of perfectly constant composition and containing over 60% of iodine. This is called "thyroxin", and has been identified as an indole compound and has been made synthetically. Given in even minute doses, relieves the symptoms of myxoedema and given in excess inducts symptoms like exophthalmic goitre and greatly affects the energy of metabolism. KENDALL believes this substance to be the true hormone of the thyroid gland and to be associated with the metabolism of amino acids. For if this thyroxin is given alone, it appears to have no direct action on the pulse rate whereas if food is taken, and particularly amino acids are ingested, there is a marked acceleration of the pulse.

There is a good amount of sodium chloride in the colloid material, also phosphorus and sulphur are constant, whereas traces of arsenic and bromine have also been detected.

THE/

THE FUNCTIONS of the THYROID GLAND.

In the past numerous hypotheses were framed to account for the presence of the thyroid, most of them are fanciful and far fetched. Some surmised that the gland was seated in the neck to give a shape-ly roundness to the contour, others that it was a covering to the important vessels in the neck, others thought it had important relations with the larynx and it, in some way, was connected with the quality of the voice. Some impressed by the number, size and tortuosity of its blood vessels, concluded that the thyroid was a safety valve regulating the blood supply to the brain. It was alleged by others that there was a close relation between the thyroid and the female sexual organs for is there not a variation in size at the menstrual periods or under the influence of sexual excitement and the greater frequency of thyroid disorders in the female sex. Others again supposed the gland had special relations with the emotional nervous system, swelling or shrinking under such influences as rage, joy or sorrow. Then later the hypothesis was framed regarding the gland as a producer of some substance of use in the bodily economy.

In/

In several ways our present knowledge of the function of the gland has been obtained by the study

- (a) of the effects, immediate and remote, of experimental removal of the gland in various animals;
- (b) of the effects of complete removal of the gland in human beings, usually on account of goitre;
- (c) of the symptoms of cretinism and myxoedema, in which the gland is absent or atrophied;
- (d) of the effects of the internal administration of thyroid substance in healthy conditions as well as when the gland is absent or functionally deficient.

The functional importance of the glands was conclusively proved when the remarkable body changes present in cases in which the gland was absent or defective were found to disappear under the influence of thyroid feeding. The train of symptoms presented by cases with atrophied thyroids was observed to follow complete thyroidectomy and to be obviated by thyroid feeding. The functional importance of the gland is greatest in early life, as shown by the profound alteration in the body which is associated with the absence of the function of the gland at the period and by the much more serious results of experimental thyroidectomy in young animals.

Thus the results of thyroidectomy seen in adults takes the form of thickening and dryness of the integument with a tendency to loss of hair.

Adiposity/

Adiposity due to deposition of a substance resembling mucus supervenes later, though at first there is some wasting. The muscles lose tone and are weaker than in the normal animal. Degeneration of tissue is retarded. Anaemia is usually present. The body temperature is low, the power of heat regulation by means of the skin, according to LORRAIN SMITH, is diminished. The sexual functions are interfered with. The limit of carbohydrate assimilation is raised. The nervous system is markedly affected, dullness and apathy being prominent symptoms. Many nerve cells, especially those of the cerebral cortex, exhibit a shrunken appearance and present a strong contrast with those of a normal animal.

Similar symptoms are observed in cases of spontaneous atrophy or degeneration of the gland in children. There is an arrest of growth especially of the skeleton, the cartilagenous bones long remaining incompletely ossified. The development of the generative organs is much delayed. The integument swollen, the surface of the skin is dry, the hair tends to fall out and becomes thin. The face is puffy and pale, the abdomen swollen, the nose depressed, the hands and feet are podgy. The fontanelles of the skull remain open, the muscles are weak and limp. Deaf mutism is common.

The/

The highest functions of the nervous system remain undeveloped, the child becomes idiotic, this seems to be due to an arrested development of the cells of the cortex cerebri. The above combination of symptoms forms the condition known as cretinism. This may be either sporadic or endemic. The former is generally associated with absence or early atrophy of the gland, the latter with goitrous degeneration. The symptoms do not show themselves until some little while after birth, in spite of the absence of a thyroid; the absence appears to be compensated by the internal secretion conveyed from the mother's thyroid to the child before birth through the placenta, after birth through the milk.

If in the adult atrophy of the thyroid occurs or there has been a too free removal in the operation of thyroidectomy, such degenerative changes take place in the gland and materially affect its functions and the condition known as myxoedema becomes manifested - the symptoms have been described in detail already. The above symptoms, whether due to congenital atrophy or operative interference, can be allayed or entirely removed by successful implantation of pieces of thyroid, an operation which has rarely succeeded in/  
in/

in the man, or by administration of thyroid extract either hypodermically or by mouth or by giving thyroxin. If the treatment is intermittent the symptoms almost at once reappear. The effects therefore are obviously due to the loss of the internal secretion contained in the thyroid gland. This internal secretion in some way affects the metabolic processes of the body either directly or indirectly promoting the nutrition of the connective tissue and influencing the functions of the cells of the nervous system particularly those of the cerebral cortex.

Given by the mouth in the human subject thyroid extract lowers the blood pressure, in diabetic patients it is said to cause the opposite result and this effect lasts for several days.

Large doses are followed by tachycardia often with some irregularity; nervous excitability; flushing of the skin with the feeling of heat; increase of perspiration; an increase of nitrogen metabolism. If long continued the fat of the body is diminished and glycosuria may be caused. Alimentary glycosuria is more easily produced than normally. There is considerable wasting although the appetite is increased. There are often digestive disturbances. In extreme cases there may be exophthalmos/

exophthalmos and other effects referable to cervical sympathetic excitation, such as dilatation of the pupil and in animals retraction of the third eyelid; psychical excitement, sleeplessness; tremor of the limbs: in short most of the symptoms of exophthalmic goitre.

The wonderful improvement in the disease called myxoedema, following the feeding of patients with thyroid gland, opened up a new chapter in the history of medicine. A whole host of men in every country of the world, have been working at the functions of the thyroid glands and the methods of procedure of its various activities. It is interesting to note that Professor Sir E.A.SCHAFER was the first to use the intravenous injection of thyroid extract experimentally and much work has been done in our School by him and his confrères on the endocrine organs.

It has long been known that the thyroid is one of the ductless glands and had an internal secretion, the gland was the first to be credited with an internal secretory function. There is a great difference between the external and internal secretions, some glands as the ovary testis and pancreas have both. The external secretions, the active principles of which are always in the nature of a ferment and are known as enzymes, they are protein in nature and are/

are readily destroyed by heat in the presence of water. The active materials of the ductless or endocrine organs, of which the thyroid is one, are for the most part, not rendered inactive even by prolonged boiling, and are certainly of a far more simple chemical constitution than enzymes. They are dialysable, many of them act instantly, their actions are probably similar to that produced by the active principles of drugs, especially those of organic i.e. vegetable origin. These also operate by immediate chemical action being conveyed to the parts which they influence in solution by the circulation.

These internal secretions are chemical substances, these may be merely bye-products of metabolism such as carbon dioxide which may act on the respiratory and nerve centres, urea which may stimulate increased action of the kidneys. The list of substances included under the term internal secretions, is almost illimitable, and to restrict the special term hormone to every constituent that can affect physiological functions, as some have done, can only lead to confusion. So Professor Sir A.E.SCHAFER has coined the word "auto-coid" to designate the internal secretions which are specially produced for the purpose of controlling metabolic functions and these are/

are of two kinds:-

(a) excitatory or hormones,

(b) inhibitory or chalones.

The autocoid of the thyroid acts like a hormone in increasing the activity of certain cells, especially nerve cells and this is particularly well seen in the sympathetic nervous system.

The problem of the discovery of the autocoid of the thyroid is complicated by the interaction and interdependence of all the internal secretions of the endocrine organs, as they are definitely correlated. Thus at puberty and at menstruation a temporary enlargement of the thyroid has been known from early times, and in all mammals we invariably find the thyroid considerably increased in size during the early stages of pregnancy, and the enlargement is found to be due to the storage of colloid in the vesicles. The thyroid secretion is associated with the integrity of the function of conception just as it is with that of menstruation.

The important influence exerted by the thyroid secretion on nutrition generally, is no doubt responsible for the fact that hardly any organ in the body remains unaffected as a result of its complete removal or atrophy. But the profound effect on the secretory organs is that which we are now more concerned with. In young thyroidectomised animals  
and/

and in cretins the generative glands are only slowly or imperfectly developed, the resulting condition being characteristically one of sexual infantilism. In the adult dog there is diminished activity as far as the production of spermatozoa is concerned. In adult rodents the removal of the thyroid calls for a response from the ovary and conversely the removal of the ovary, a distinct change is seen in the thyroid, the vesicles being greatly distended with colloid, further one notices the colloid is basophil in character and therefore stains blue with haematoxylin instead of pink with eosin, whereas in the normal thyroid the colloid is acidophile. It may be safely asserted that there is considerable increase in the functional activity of the thyroid as far as colloid production is concerned and probably the autocolloid, in rodents after oophorectomy.

There is a definite relation between the endocritic system and the genital functions, the thyroid, pituitary and adrenals influence development and subsequently preserve the integrity and activity of the genital organs. Also all the endocrine/

endocrine glands acting in harmony control the metabolism in response to the necessities of the genital functions, but in addition they adapt the whole organism to the possibility of selection and regulate the secondary characteristics, both physical and psychical, to suit the needs of the individual. Excessive thyroid and ovarian secretion lead to an unusual excretion of lime salts and BLAIR BELL has put forward the theory that calcium retention is a characteristic of masculinity. There are changes in the endocrine glands during pregnancy when calcium is needed for the foetus, these in the non-pregnant woman produce masculinity which is seen in myxoedema.

At the menopause when the reproductive function ceases, there are retrogressive changes in the thyroid and the adiposity which ensues is due to a reduction in the activity of the gland, as well as a coincidental insufficiency of the ovarian internal secretion.

The thyroid secretion produces an increase of excitability of those tissues which are amenable to the action of adrenalin. On the other hand when the thyroid is extirpated the activity of the secretion of the adrenals is diminished/

diminished and the phenomena which are normally produced by the sympathetic stimulation are similarly affected. Further with hyperthyroidism such as occurs in intense feeding with thyroid, most of the symptoms are those of over excitation of the sympathetic and are similar to those caused by adrenalin. There is, moreover, some evidence that the amount of adrenalin in the blood is increased both in hyperthyroidism and in exophthalmic goitre. So apparently thyroidectomy stimulates the adrenal cortex to excessive secretion and this also tends to produce calcium retention and prevents secretion.

After the removal of the thyroid the pituitary becomes generally altered and enlarged especially the pars anterior in which it is not uncommon to find that a certain number of the vesicles contain colloid, not unlike that of the thyroid, - this colloid material, however, does not contain iodine. It is said that this increase of the pituitary after thyroidectomy does not occur if thyroid extract be administered. The increased activity of the pars intermedia of the pituitary is also quite plain. These facts would at first sight seem to indicate that the pituitary and/

and the thyroid can act vicariously but this is very doubtful for it has not been found that pituitary extract has any beneficial effect on the treatment of exophthalmic goitre and myxoedema. Nevertheless the association in function of the two glands must be more or less close, not alone for the above reasons but also because they both associate too much the same degree with the sexual organs and both act on the higher functions of the nervous system in much the same manner. With regard to the thymus, some believe that there exists a mutual relationship between the two organs and that they exercise, by their internal secretions, an excitatory influence upon one another. In confirmation of this it has been stated that increase or diminution in size of the two organs frequently go hand in hand, but this can only be in early life, for under normal conditions of growth and development the thymus is undergoing retrogression whilst the thyroid is becoming more active in its function. Moreover the normal variations in both organs are so considerable and at present in spite of many observations so little is known regarding the conditions under which they occur that it will be wise to reserve judgement as to their mutual relationship. However/

However the thymus is enlarged and persistent in exophthalmic goitre.

Experimentally in the cat and rat fed with thyroid glycogen disappears from the liver, but there is no glycosuria, the sugar having been conveyed to the tissues and oxydised. So to put it succinctly the thyroid produces mobilisation of the carbohydrates. Thyroid feeding also tends to diminish the limit of assimilation of sugar, this may be either due to an increase in the secretion of adrenalin or to a direct inhibitory effect on the internal secretion of the pancreas.

THE/

THE FUNCTION of the INTERNAL SECRETION.

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As stated above the autocoid of the thyroid acts as a hormone increasing the activity of certain cells especially nerve cells and this is markedly seen in connection with the sympathetic system. The question arises, has this a direct effect on the sympathetic system, or is it indirect through the adrenals which are stimulated to increased secretory activity by excess of the thyroid in the blood. The answer is not easy. But it may be stated that although certain symptoms of hyperthyroidism are similar to those produced by excess of adrenalin in the blood, others are not so. This is the case with flushing of the skin which is due to vascular dilatation, whereas adrenalin ordinarily produces vaso-constriction. Further excess of adrenalin in the blood leads to glycosuria which is not as a general rule seen in exophthalmic goitre nor in glycosuria a necessary result of thyroid administration. Moreover it is undoubtedly the case that the administration of adrenalin exercises a beneficial effect in some cases of exophthalmic goitre, a fact which would be inexplicable on the theory that the results of hyperthyroidism is simply/

simply due to excitation of the adrenals and the product of an excess of adrenalin. But although many of the effects of thyroid feeding and of hyperthyroidism otherwise produced can be explained by the presence of excitatory or hormone autocoids, it is not possible to explain the results produced by thyroid deprivation or hypothyroidism upon the body generally and certain organs in particular, merely by assuring the absence of these excitatory substances. For the loss of the thyroid is followed by increased growth and presumably increased activity of certain other organs of the endocritic system mentioned above. This is the case with the pituitary and although it has been suggested that this is an instance of vicarious increase in size associated with the performance of similar functions the similarity of function of the two glands is far from obvious. Another probable explanation is that besides a hormone that excites some cells, the thyroid secretes an autocoid of chalone nature which restrains the activity of others, on the removal of the thyroid, this restraint is abolished and over activity is the result in the other gland. This however is in the realm of pure hypothesis and much work will have to be done to prove this theory.

Thus/

Thus to sum up the physiology of the thyroid, we see that the thyroid is essential to life, it governs the building up and growth of all cells and with thyroid insufficiency, there will be defective growth and this will be most noticeable in the young subject, where not only is growth lessened and macroscopic growth diminished, but cells fail to reach their proper development and the connective tissue remains myxomatous. Whereas excessive activity produced by experimental feeding with suitable preparations of the thyroid is shown by excessive metabolism, decrease in weight, not only from destruction of fat but also of proteids, increase in growth of long bones in young animals and various nervous symptoms affecting the heart as tachycardia and palpitation, the central nervous system irritability and sleeplessness, and the peripheral nerves and muscles, such conditions which are seen as symptoms of exophthalmic goitre. It regulates the destruction of the protein molecule, it is kabolic in its action, also it governs the elimination of the waste products of katabolism, thus in the adult if there is an insufficiency of thyroid secretion there will be an accumulation of material which should be katabolised. It controls calcium metabolism/

if the diet is persisted in, pathological effects may be produced. These are evidenced by some degree of cell exhaustion from continued hyperactivity which may lead to symptoms of subthyroidism. Then again the thyroids restored by increased physiological action in mental and emotional states to which the healthy human being is subjected, such as anger, fear, love, grief, anxiety, great mental exertion as well as in a condition of physical exertion.

The gland is controlled by the sympathetic, and the brain cannot involuntarily inhibit its activity. The excess or defect of the thyroid activity in relation to katabolism are so in evidence in adult life that McCARRISON has compared its role in the living organism to that of the draught on the fire. On the other hand GUDEVACH'S work reminds us of its influence on anabolism, and he has shown experimentally that feeding tadpoles on thyroid may increase the rate of growth four times. Professor Sir ARTHUR KEITH believes that the endocrine glands may help to determine racial characteristics and suggests that the mongoloid facies in human evolution is dependent on thyroid peculiarities due perhaps in the first instance to some climatic or geographical factor and perpetrated by heredity.

E T I O L O G Y .  

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F R E Q U E N C Y .  

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Exophthalmic goitre used to be looked upon as a rare disease, but nowadays when walking about this city or any other large city, one sees the typical facies of this disease very frequently, and the disease seems to be on the increase. When I was in the United States of America last year, I noted that this disease was more frequently met with than in our land. When discussing this disease with Dr. Plummer and others of the Mayo Clinic, all said that the type of the disease was more severe and seen at an earlier age than it was seen in Great Britain, the reason given was, that life was more strenuous in the United States, also that there was more stress and strain upon the nervous system, than in the older and more established countries.

S E X .  

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Women are more subject to Exophthalmic goitre than men and from studying the reports of cases collected by various physicians on the continent, in /

in America including Canada and the United States, there is no doubt that the proportion of the two sexes varies considerably in the various countries. CHARCOT said the disease was only a little less frequent in men than in women, others say the proportion is 9 females to 2 males; in this country the proportion is given as 10 to 1 and in my limited experience I would put the proportion as 13 to 1. The greater proportion of females is the more significant when we remember the evidence of association between the thyroid gland and the organs of generation and that the disease, especially in women, is during the sexual period.

#### AGE.

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The disease may occur at any age, cases have been observed in childhood from the third year onwards, but these are very rare. During the summer I had a patient under my care, a married woman of 59 who was suffering from exophthalmic goitre.

Most cases occur between 16 and 40, that is between puberty and the meno-pause in women. After 50 the incidence is rare and then men are relatively more often affected. The commonest age is between /

between the second and third decade.

### MARRIAGE.

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The question of marriage as to the etiology is a debatable one, equally eminent obstetricians have made diametrically opposed statements and all one can say is, that the disease arises during pregnancy. Sometimes exophthalmic goitre begins in pregnancy in the puerperal period or later. On the other hand many patients improve during pregnancy and do not relapse afterwards. If the condition of the patient is not too serious pregnancy is an advantage to the patient.

Diseases of the pelvic organs do not have any definite bearing on the occurrence of the malady, nor are menstrual disorders specially concerned with the condition, though leucorrhoea is a very common and intractable symptom.

### SOCIAL ORDER.

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The disease is relatively commoner in poorer classes, the onset is earlier, developing between the ages of 15 and 35, whereas in the richer classes the age of onset is prolonged over a further period of 10 to 15 years. Nearly twice as many cases arise in the earlier years of sexual life in the poor /

poor as in the richer class of females. It may be that nutrition plays an important part in the genesis of the disease in females of the poor classes.

OCCUPATION seems to be unimportant in the etiology as regards women. Though during the training of recruits in America, before they came over and underwent the hardships and nervous strain of service in the front line trenches, many cases of hyper-thyroidism were noticed and treated. It has also been noticed that men such as engine drivers, station masters or others placed in situations involving mental strain, seem to suffer from this disease, though I have hunted through the literature on this subject I have never found any tables showing the predisposition to particular occupations.

FAMILY HISTORY is unimportant in many cases, though a continental physician has put on record that, in one family he had under his care, 7 cases of exophthalmic goitre occurred among the 16 members of the family in 3 generations. Another states that in a family of 8 children out of a family of 10 and 3 grand-children, were all subject to this disease. Personally in all the cases I have had under my care, there has never been any family history suggestive of definite exophthalmic goitre, nor even of hyperthyroidism./

thyroidism. The tendency to this malady seems to be transmitted by the males.

In goitrous regions goitres are often found among mothers and sisters of patients who have exophthalmic goitre, occasionally an immediate relative as mother, sister or brother has the disease. It has been suggested that the occurrence of simple goitre, often unnoticed, among the relatives of the patient, as suggesting a congenital alteration of the thyroid, can be converted into exophthalmic goitre, by the influences of infection such as typhoid fever, syphilis etc. In districts where endemic goitre prevails the exophthalmic form is also more common than in other parts; this is true of the regions of the Great Lakes in America, and in Switzerland and France. The malady is often consequent upon acute disease and a number of cases appear to have followed an attack of influenza. During the last great epidemic of influenza, many drew attention to the frequency of hyperthyroidism especially during the convalescent period.

Chlorosis was always mentioned as a cause when the disease was first discovered, but now it is recognised that the condition is a pseudochlorosis.

Some/

Some throat, tonsillitis or other acute infections such as typhoid fever, smallpox, measles, pneumonia, rheumatic fever, mumps, etc, often precede the symptoms of exophthalmic goitre and thyroiditis is often secondary to some infection. This is one of the arguments to put forward proving that this disease is caused by an intoxication. The ancients called attention to the fact that in the adult female the thyroid gland may temporarily become enlarged under the influence of excitement and the fact is well known now.

The relations of locality and climate are obscure, the incidence seems to vary in different parts of the world, being higher in England and on the sea coast than on the continent. America has a higher pregnancy than Europe.

The frequent occurrence of exophthalmic goitre in nephritics is estimated at 3%, occurring as one would expect, in sub-acute and chronic nephritis.

In America especially it has been observed that among etiological factors, there is the presence of syphilis in 55% of cases, inherited syphilis is looked for and ruled out in all cases. This has not been my experience and I have found syphilis/



syphilis is extremely rare and when it has occurred it has been an accident and not the cause.

Tubercular disease, some physicians in the United States state as the cause, and put the percentage as high as 18% of cases. Here again this has not been my experience and in looking up the literature on the subject, I find that tuberculosis is only mentioned as a cause, as this disease has sometimes been found in the thyroid at post mortems. But one has to be careful for the frequency with which exophthalmic symptoms are seen in tuberculous patients may lead to a grave error in diagnosis, and thus early cases of pulmonary tuberculosis are missed and wrongly treated. Perhaps this enlargement of the thyroid may be of toxic origin for enlargement of this gland appears as a complication of tuberculosis. In cases of tuberculosis with exophthalmic goitre symptoms, the treatment of the thyroid may favourably influence the course of the pulmonary lesion even to full recovery.

Trauma seems to be a cause, for cases have been reported of this disease coming on after an accident, but these cases are on a par with fright which gives rise to continuous excitation of the sympathetic nervous system.

In/

In the past, fright has always been looked upon as the cause of exophthalmic goitre, and no doubt this view is assisted by the resemblance of the typical facies to fright, also the close connection between some of the chief symptoms of this disease and the more immediate effects of terror, such as the heart beating quickly and violently, so that it palpitates or knocks against the ribs, there is trembling and tremor of all the muscles, the eyes start forward and the uncovered and protruding eyeballs are fixed on the object of terror, the skin breaks out into a cold and clammy sweat, the face and neck are flushed or pallid, the intestines are affected. Often the actual disease is ushered in by a fright, but careful enquiry so often discloses the probability of the disease being in existence in a mild or latent form before the shock. In the last case I had under my care, the exciting cause was a fright, the patient's father, an old man of 90, caught his foot on the carpet whilst walking and fell, he did not fracture his femur, but the daughter had to be treated for violent palpitation at the same time as the father, and later exophthalmic goitre developed. In going into the history carefully, I found that there had been attacks of tachycardia/

tachycardia for some months previously , also tremors and an indefinite history of diarrhoea with offensive stools, the offensiveness was a marked feature, this diarrhoea had been present off and on for at least two years.

When all this has been said there are cases of exophthalmic goitre in well marked forms which rapidly follow a severe and sudden shock to the nervous system, and this suggests the starting point of the disease may be a derangement of the emotional nervous system and that with this there is sooner or later associated an altered or perverted condition of the thyroid gland, which serves to keep up many of the characteristic symptoms. A French physician Léon Béraud by name, writing about the relation of the war to exophthalmic goitre, states that since 1914 he has met with a relatively large number of cases in men from 20 to 45 years of age. Some of the subjects had previously had small stationary goitres for a more or less prolonged period. Exophthalmic symptoms developed from physical or mental overwork, intoxication from poor food or water or microbic infection, dysentery, typhoid paratyphoid in forms of light attacks of thyroiditis. Cases of exophthalmic goitre appeared suddenly following/

following violent emotions, repeated anxiety, strenuous physical exertions showing all the typical symptoms. Nervous shock manifested essentially in vasomotor disturbances and transient or permanent changes in the ductless glands and central nervous cells is held to be the starting point.

Whilst in London a few months ago, I was discussing this subject with one who is on the staff of the London Hospital, and he said that this disease was certainly more often seen now and gave the cause of this frequency to the numerous air raids that the people of London suffered from during the war.

CRILE in America and others, in trying to find out the *raison d'être* of shock, have come to the conclusion that the sympathetic system is affected, and that it is designed as an intensive preparation for action or defence. Thus if the response that the sympathetic nervous system gets is not used in this way, it is dissociated, perverted or prolonged as to produce through the thyroid gland exophthalmic goitre with its danger to life. The evil effects of depressing emotions, of anxiety, fear pain and anger receive an explanation when we see that through the sympathetic nervous system they can lead /

lead even to structural change. In this disease we have the continued action of some excitant which admits of no period of rest, so that the gland is soon emptied of its colloid reserves whilst the secreting structures undergo compensatory hypertrophy. The heightened excitability of the sympathetic nervous system is shown in this malady due to contraction of the protractor bulbi muscle, the rapid pulse, the sweating and also the diminished secretion of gastric juice. As with adrenal stimulation increased blood pressure, a tendency to glycosuria and pigmentation of the skin. CRILL has suggested that the primary cause is the action on the adrenals with the pouring out of the adrenalin which in its turn acts on the thyroid and because the sympathetic nerve supply is like a cistern with its tap turned on and cannot be turned off. The stimulation of the whole emotional apparatus is so obvious that the aspect has been well compared to a state of continuous fear as seen in the staring eyes, the downward curve of the mouth and the tremors.

There is a remarkable lowering of the brain thresholds to stimuli of all kinds. According to CRILL the response to emotional, infective and noci-ceptor stimulation are all equally exaggerated and he describes similar changes in the brain cells produced /

produced by exophthalmic goitre, fear, shock and exhaustion. The continuous action of the sympathetic appears to lead to degeneration in the superior cervical ganglia also for pigmentation, chromatolysis, atrophy and fibrosis were found.

But exophthalmic goitre is not only caused by increased irritability of the sympathetic nervous system, there must be also a "status degenerativus" and this is where the psychic element also comes in as a causal factor of the disease.

There are two schools of thought, one says that exophthalmic goitre is caused by the constant stimulation of the thyroid through the sympathetic nervous system and it is not true that the cause of the disease is abnormal functioning of the thyroid, but that the thyroid manifestation is, rather, a result merely of an augmented sympathetic activity as are many of the exophthalmic symptoms.

The other school say that the disease is caused by the autocoid of the thyroid acting like a hormone increasing the activity of certain cells especially nerve cells. This increase in excitability is specially well marked in connection with the sympathetic nervous system. This may be not only an academic question but it may lead up to the discovery of the primal cause of the disease which is still wrapt in obscurity.

It/

It is generally conceded that the symptoms of this disease are caused by the thyroid secretion and the etiological relationships between exophthalmic goitre and the thyroid cannot any longer be doubted, whether the etiological factor is to be found in simple increase of secretion, that is hypersecretion, or a perverted secretion is not so easily answered. But the consensus of opinion is leaning towards a hypersecretion because :-

- (1) the symptoms of the disease are not unlike those produced by hypersecretion of the thyroid administered in a normal individual and in this connection it is interesting to note the following case, a man of 43 years of age, without neurotic antecedents took about 1000 gr. 5 thyroid tablets for obesity in six weeks. By the 3rd week he had thyroid enlargement of about 3 cm. Dyspnoea, palpitations of the heart with bounding carotids, depression and mental excitement with insomnia following. A warm skin, moderate exophthalmos and tremor were present, but the thyroid although distinctly enlarged was free from thrill and murmur. The pulse was 120, the apex of the heart forcible and displaced outwards. STELLWAGS and VON GRAFE'S signs were present. There was glycosuria. Recovery followed rather rapidly when the medication was discontinued but the exophthalmos and eye lid signs persisted for 6 months.
- (2) The symptoms of disease in general are opposite in character to the symptoms found in cases where the thyroid is atrophied.
- (3) The blood in a person with exophthalmic goitre when injected into mice increases the resistance to the toxic action of acetone nitrill which is also the case after thyroid extract has been injected.

(4) /

- (4) The signs of hyperactivity of the thyroid are seen in stained sections of the gland under the microscope.

Certain investigators, however, deny that it has yet been conclusively demonstrated that exophthalmic <sup>^</sup>goitre is due to hypersecretion of the thyroid. It is pointed out that if hypersecretion was the cause of the disease, one would expect that the injection into animals, of the blood from patients suffering from it, would produce symptoms similar to those following the injection of thyroid extract. The results of such experiments, however, have been extremely confusing and very indecisive since it is difficult to recognise in the laboratory animals, many of the characteristic symptoms especially those affecting the skin and general bodily nutrition. Another difficulty in accepting the hypersecretion hypothesis is said to be the fact, that an extract of a gland removed from an exophthalmic <sup>^</sup>goitre patient has no different physiological action on a normal animal from an extract of a normal gland containing the same percentage of iodine. The evidence is by no means conclusive, one way or the other, and it may be well that the observed changes in the thyroid gland are not the cause of the symptoms of exophthalmic <sup>^</sup>goitre/

goitre, but merely like other symptoms of the disease, a result of some condition elsewhere. In this connection it is interesting to note that degenerative and pigmentary changes in the ganglion cells of the cervical sympathetic have been found in cases of exophthalmic goitre and which are believed to be distinctive of this condition. On this account disease of the sympathetic nervous system is suggested by some as the possible cause of the cardiac and ocular symptoms as well as the thyroid activity, the latter produced secondarily, however, it is supposed that the metabolic phenomena seen are characteristic of the disease.

After the results published by McCARRISON on his findings on the cause of endemic goitre, one's thoughts have been centred on auto-intoxication especially from gastro-intestinal toxaemia and McCARRISON believes strongly that this is the cause of the exophthalmic variety also. He says the ideal conditions for the development of this disease are provided when all three classes of factors, nutritional, psychic and infectious, operate on the individual at the same time or where two of them do so. They are predisposing causes only which favour the action of the underlying causal agency. The agency is one which gives rise to continuous excitation of the sympathetic nervous system. That symptoms similar/

similar to those of exophthalmic goitre can be induced by continuous excitation of this system is shown by the experiments of CANNON where the phrenic-nerve was joined to the peripheral portion of the cut cervical sympathetic in the cat. The operation resulted in tachycardia, increased excitability, loose motions, exophthalmos on the operated side and an increase of the body metabolism as well as an increase in the size of the adrenals. In seeking for the source of the excitant of these symptoms of exophthalmic goitre, one is reminded that effects similar to those caused by stimulation of the sympathetic nervous system are produced by certain amines resulting from the putrifactive decomposition of proteins or amino acids in consequence of bacterial action, and this has been proved by Professor G. BARGER. The most common source of the amines is the gastro-intestinal tract. According to KENDALL of the Mayo Clinic, the active constituent of the thyroid secretion is an indol compound of iodine, which he calls alpha-iodine. It is a suggestive fact that indol is a putrifactive decomposition product of the tryptophane in the protein molecule.

A further method of investigation to which it is necessary to refer, is the routine examination of the faeces in all cases of exophthalmic goitre by every means at our disposal, and where possible their bacteriological/

hacteriological examination for the detection of organisms to which the patient's resistance is low.

I was able to carry out some investigations on these lines on two patients, and these are instructive; but the number of patients I was able to examine in this way was far too small to make any deductions from, and one would require at least a series of 50 patients in order to make the report of any value.

The routine was this; the patients were kept in bed and made to rest in the physiological sense, free from all burdens, cares and household duties. The diet was not restricted except in this one particular, meat was only allowed once a day and then at mid-day. Two and a half pints of warm water was injected using a Higginson's Syringe with a long nozzle, so as to get the fluid as high up into the colon as one could. This was passed, and it was collected into a glass jar and put aside. Then another two and a half pints was injected in the same manner, when the last of the first injection had been passed, and this usually worked out at about 25 minutes afterwards. When the second injection was passed, this was also collected and put aside in a glass jar. If the douching is properly carried out, the second jar should contain no faecal matter, and should be quite clear, but it is difficult to train nurses/

nurses to wait till all the first injection has been passed before injecting the second two and a half pints, so in the tabulated results that follow, though the second wash out was always clearer than the first wash out, yet none were as clear as I should have liked to have seen them. For the matter of convenience this was done at night before the patient went to sleep and I saw the resultant next morning about 10 A.M. and examined it.

The two patients that I carefully examined and wish to report on, were treated in the above mentioned manner, and have been bacteriologically examined.

One patient was a man, a motor mechanic aged 32, who had been discharged from the Army as unfit. He had a dilated heart when he joined up, and was put into category B III; however he was sent to France, and drove a motor lorry carrying rations and ammunition right up to the forward dump nearest to the trenches, thus he was constantly under shell fire. His history was good, except for the condition of his heart. He and his two brothers run a motor hiring business in Dalkeith; he lived a strenuous outdoor life, working often 16 hours a day driving his motor car when wanted. In the army he had an excellent history; he never was on sick parade nor in hospital /

hospital till he began to feel nervous and have tremors with attacks of palpitation, then he reported sick, was sent down the line, sent home, boarded and discharged from the army. Patient is a tall man, 6 feet 1 inch in height, showing all the typical signs and symptoms of exophthalmic goitre. The enlargement of the thyroid is specially noticeable, and I measured it. Take the 7th Cervical Spine as the fixed point behind, going round the most prominent part of the enlarged thyroid - this measured 18 inches. His weight was 9 stone, whereas his usual weight was 13 stone.

The second patient was a woman aged 59, who received a great shock when her husband, who left for business in his usual health at 9 a.m., was brought back at 11 a.m. having been knocked down and killed by accident. She was a poorly nourished old lady with a small goitre, very little exophthalmos, but suffered from tachycardia, loss of sleep, and symptoms of the nervous type - this patient was very unsatisfactory.

The examination of the faeces consisted of naked eye examinations of the two wash outs. Microscopic examination of Gram stained films, a loopful of the second wash out was taken after the contents of the glass jar was stirred up and put upon a glass slide - dried and stained in the ordinary/

ordinary way. A rough count of the bacteria was taken in this way; I used to imagine all the bacteria collected together, and took this as the average field content - at present it is impossible to be absolutely scientifically accurate in counting either the number of the bacteria in each colony or the number of the colonies in a given portion of a stool for so much depends on the dilution, consistency and time of the examination. The method I used has no standard except the one that each observer makes for himself and though not strictly scientific it is sufficiently accurate to be a guide. Also a culture was taken on Agar incubated at 37<sup>o</sup>C. for 24 hours, examined by naked eye, the various and different colonies were picked off, stained and examined. The urine was also bacteriologically examined, a sterile specimen was drawn off with a sterile catheter from the female patient. In the male patient I did not feel that it was right to pass the catheter, so this method was not used, but with ordinary precautions a specimen, to all intents and purposes sterile, was obtained. Before passing urine, when a specimen was wanted, I personally washed the glans penis and the meatus with a swab dipped in a lysol solution and then with sterilised water, the patient was told to pass water and to take/

take a portion in the middle of the act of micturition pass it into a sterilised test tube, and finish the act, thus aseptic and antiseptic precautions were taken. A portion of this urine was examined and put to the usual urinary tests, and the rest was put into an equal quantity of broth consisting of meat extract, peptone and salt, incubated at  $37^{\circ}\text{C}$ . for 24 hours. A loopful of this was spread upon agar incubated again at  $37^{\circ}\text{C}$ . for 24 hours, stained and examined under the microscope.

A control was taken for the patient, a man aged 50, Clunie by name, and suffering from emphysema and bronchitis. Unfortunately I had great trouble with the female patient, and I had to cease my observations upon her, because she refused to have her urine drawn off, and I found the double enemata was causing her pulse to increase in rate, her temperature to rise slightly and she did not sleep at night after these injections, thus after one examination I had perforce to cease the examination of her faeces and urine.

Details/

C. PATIENT

14/6/21 Naked eye characteristics.

1st WASH OUT

SEDIMENT 2/5 of jar contents.

COLOUR (1) of sediment light brown.  
(2) of fluid lighter brown.

ODOUR + + + (maximum + + +)

REACTION to Litmus, acid.

No Scybala

2nd WASH OUT

SEDIMENT 1/3 of jar contents.

COLOUR (1) of sediment light brown.  
(2) of fluid light brown lighter than in 1st W.O.

ODOUR + + +

REACTION to Litmus slightly acid.

MICROSCOPIC/

C. CONTROL

N. E.

1st W. O.

SEDIMENT 1/5 of jar contents.

COLOUR (1) of sediment yellow brown.  
(2) of fluid brown

ODOUR + less ammoniacal than 2nd W.O.

REACTION to Litmus slightly acid.

No Scybala.

2nd W. O.

SEDIMENT 1/10 of jar contents.

COLOUR (1) Sediment buff.  
(2) fluid lighter in colour and fairly clear.

ODOUR not offensive somewhat ammoniacal.

REACTION to Litmus neutral

---

 MICROSCOPIC EXAMINATION of 2nd WASH OUT ONLY
 

---

AVERAGE FIELD CONTENT 45%  
 GRAM POSITIVE Diplococci a few, some large resembling Enterococci. Cocci, a few. Bacilli make up 85%, some large resembling Lactic Acid Bacilli

A. F. C. 30%  
 GRAM POSITIVE Diplococci one or two. Cocci a few scattered thro'out the slide Bacilli make up 99% of gram positive organisms, variations in length and breadth - some large which resemble Lactic Acid Bacilli.

GRAM NEGATIVE Coccal bacillary forms probably B. Coli - these show variations in size.

GRAM NEGATIVE Coccal bacillary forms probably B. Coli - variations in size.

SPIROCHAETES very numerous three or four on every field - these resemble Vincent's.

No SPIROCHAETES seen.

No Yeast cells seen.

No Yeast cells seen.

Undigested food + (maximun +)

Undigested food +

In an average field  
 Gram Positive 25%  
 Gram Negative 75%

In an average field  
 Gram Positive 50%  
 Gram Negative 50%

---

 URINE STERILE.
 

---

Sp. Gravity	1026	1020
Colour	light amber	amber
Albumen	none	none
Bill	none	none
Blood	none	none
Sugar	none	none

URINE/

---

C.  
URINE CONTINUED.

MICROSCOPIC EXAMINATION of CENTRIFUGED SPECIMEN.

R.B.C. few.  
Pus cells +  
Epithelial cells few,  
Bacteria + motile  
  
No casts  
Crystals calcium oxylates  
seen.

C.  
R.B.C. one or two.  
Pus cells +  
Epithelial cells few  
Bacteria + + all  
motile.  
No casts.  
Crystals calcium  
oxylate.

CULTURE

Naked eye appearance,  
very abundant growth of  
staphylocoecal colonies

extensive growth  
grey colonies of B.  
Coli.

MICROSCOPIC

Staphylococci pure culture  
showing some variation in  
size.

chiefly made up of  
B. Coli a few stap-  
lylococci seen.

17/6/21

FÆCES.

N. E.

1st W. O.

ODOUR + +  
SEDIMENT  $\frac{1}{2}$  of jar contents  
COLOUR of Sediment light  
brown,  
of fluid lighter  
brown.

REACTION to Litmus neutral

No/

N. E.

1st W. O.

ODOUR +  
SEDIMENT  $\frac{2}{5}$  of jar  
contents.  
COLOUR of sediment  
brown,  
of fluid  
lighter in  
colour.

REACTION to Litmus  
acid.

No Scybala.  
Mucus +  
Undigested food + +

2nd W. O.

ODOUR +  
SEDIMENT 1/5 soft pultaceous.  
COLOUR of Sediment dark brown.  
Of fluid same colour as sediment.  
REACTION to Litmus alkaline.

MUCUS +  
Undigested food +

MICROSCOPIC EXAMINATION of 2nd WASH OUT ONLY

A. F. C. 50%

GRAM POSITIVE Diplococci not numerous, some large resembling Enterococci.

Cocci a few.

Bacilli numerous major portion of field - vary in size, large resemble Lactic Acid Bacilli.

GRAM/

No Scybala.  
Mucus.  
Undigested food +  
There was less fluid in No. 1 jar than in No. 2.

2nd W. O.

ODOUR - not offensive.  
SEDIMENT 1/5 of jar contents.  
COLOUR of Sediment biscuit.  
Of fluid lighter brown.  
REACTION to Litmus slightly acid.

MUCUS.  
Undigested food + +

A. F. C. 25%

GRAM POSITIVE Diplococci one or two - some large resemble Enterococci.

Cocci a few.

Bacilli, the majority of the field vary in length and breadth, a few large resemble Lactic Acid Bacilli.

GRAM NEGATIVE Coccal Bacillary forms probably B. Coli

SPIROCHAETES still numerous

FAT globules seen.  
No yeast cells seen.

Undigested food +  
In an average field

GRAM POSITIVE 20%  
GRAM NEGATIVE 80%

GRAM NEGATIVE Coccal Bacillary forms show variation in size.

No Spirochaetes seen.

No yeast cells seen.

Undigested food +  
In average field

GRAM POSITIVE 40%  
GRAM NEGATIVE 60%

URINE STERILE

Sp. Gravity	1026	1018
Colour	Straw	amber
Albumen	none	none
Bile	none	none
Blood	none	none
Sugar	none	none

MICROSCOPIC EXAMINATION of CENTRIFUGED SPECIMEN

R. B. C. few.

Pus cells, one or two

Epithelial cells, a few.

Bacteria not so numerous as in 14/6/21, but still + motile.

No casts seen.

No crystals seen.

CULTURE.

N. E.

Pinpoint colonies suggestive of streptococci.

Large/

R. B. C. few.

Pus cells +

Epithelial cells few.

Bacteria + + motile.

No casts seen.

No crystals seen.

Large colonies of B. Coli predominating.

Large grey colonies of B. Coli.

Staphylococci colonies a few.

MICROSCOPIC

Pure culture B. Coli - organisms show a variation in size. No streptococci found.

B. Coli. a few Staphylococci seen amongst the B. Coli.

29/6/21

$\frac{1}{2}$  c.c. of Polyvalent B. Coli vaccine given.

1/7/21

FAECES.

N. E.

N. E.

1st W. O.

1st W. O.

ODOUR + +

ODOUR +

SEDIMENT  $\frac{1}{3}$  of jar contents.

SEDIMENT  $\frac{1}{3}$  of jar contents.

COLOUR of sediment yellow brown. Of fluid darker than sediment.

COLOUR of sediment darkish brown. Of fluid lighter than sediment.

REACTION to Litmus very slightly acid.

REACTION to Litmus acid.

Scybala.

No. Scybala.

Mucus +

Mucus +

Undigested food +

Undigested food +

2nd W. O.

2nd W. O.

ODOUR + +

ODOUR not offensive.

SEDIMENT  $\frac{3}{5}$  of jar contents.

SEDIMENT  $\frac{1}{7}$  of jar contents.

COLOUR of Sediment almost yellow. Of fluid same colour as sediment.

COLOUR of sediment light brown. Of fluid same light brown.

REACTION/

REACTION to Litmus, very slightly acid.  
No Scybala.

Mucus +

Undigested food + +

REACTION to Litmus slightly acid.  
No Scybala.

Mucus + +

Undigested food +

MICROSCOPIC EXAMINATION of 2nd WASH OUT.

A. F. C. 30%

GRAM POSITIVE Diplococci few some large resemble Enterococci.

Cocci small and large - a few in chain formation

Bacilli various sizes, large resemble Lactic Acid B.

GRAM NEGATIVE Coccal Bacillary forms probably B. Coli.

SPIROCHAETES

Mucus +

Yeast cells, a few seen

Undigested food + +

Small clear bluish cells 15" in diameter may be vegetable for there was a large proportion of undigested orange in this stool.

Long threads seen under L.P. under 1/12" look like sheads of Mucus with Bacilli adherent - some had only G. Positive/

A. F. C. 30%

GRAM POSITIVE Diplococci, not numerous some large resemble Enterococci.

Cocci a few scattered thro' the fields.

Bacilli increased in proportion more than 17/6/21 some large resemble Lactic Acid Bacilli.

GRAM NEGATIVE Coccal Bacillary forms variations in size - some Bacillary forms show bi-polar staining.

No Spirochaetes found.

No yeast cells seen.

Undigested food +

Positive and others Gram  
Negative organisms  
adherent. Not mixed.

In an average Field  
GRAM POSITIVE 15%  
GRAM NEGATIVE 85%

In an average field  
GRAM POSITIVE 30%  
GRAM NEGATIVE 70%

URINE STERILE,

Sp. Gravity	1024	1020
Colour.	amber	amber
Albumen	none	none
Bile	none	none
Blood	none	none
Sugar	none	none

MICROSCOPIC EXAMINATION OF CENTRIFUGED SPECIMEN.

R. B. C. +

R. B. C. few.

Pus cells, few.  
Epithelial cells, few.  
Bacteria + motile  
No casts seen.  
No crystals seen

Pus cells +  
Epithelial cells +  
Bacteria + motile.  
No casts seen.  
No crystals seen.

CULTURE.

N. E.  
Many colonies B. Coli  
Few Staphylococci colonies

Only B. Coli colonies  
seen.

MICROSCOPIC

Pure culture of B. Coli

Pure culture of B.  
Coli.

12/7/21

FÆCES.

1st W. O.

1st W. O.

ODOUR + + +  
SEDIMENT 1/4 of jar  
contents.  
COLOUR/

ODOUR +  
SEDIMENT 1/4 of jar  
contents.

COLOUR of Sediment brown,  
Of fluid light brown.

COLOUR of Sediment  
dark brown.  
Of fluid light brown

REACTION to Litmus neutral

REACTION to Litmus  
just acid.

SCYBALA difficult to deter-  
mine as there was much  
fluid matter floating

No SCYBALA.

MUCUS + + +

MUCUS a little not a  
plus.

Undigested food +

Undigested food +

2nd W.O.

2nd W. O.

ODOUR + + +

ODOUR not offensive.

SEDIMENT 1/4 of jar  
contents.

SEDIMENT 1/8 of jar  
contents.

COLOUR of Sediment  
yellowish brown.  
Of fluid not clear.

COLOUR of Sediment  
light brown.  
Of fluid very light  
brown almost clear.

REACTION to Litmus very  
slightly acid.

REACTION to Litmus  
neutral.

No Scybala

No Scybala.

MUCUS + +

No MUCUS seen.

Undigested food +

Undigested food +

MICROSCOPIC EXAMINATION of 2nd W. O. ONLY.

A. F. C. 25%

A. F. C. 35%

GRAM POSITIVE Diplococci  
a few, some large resemble  
Enterococci  
Cocci/

GRAM POSITIVE Diplocco-  
cci some, a few large  
resemble Enterococci.

Cocci, a few.  
Bacilli as usual  
form most of the  
field. Some large  
resemble Lactic  
Acid Bacilli.

Cocci, a few.  
Bacilli numerous -  
some large resemble  
Lactic Acid Bacilli.

GRAM NEGATIVE Coccal  
Bacillary forms, pro-  
bably B. Coli, the  
Bacillary forms vary  
greatly in size.

GRAM NEGATIVE, Coccal  
Bacillary forms show  
variation in length  
and breadth.

SPIROCHAETES very  
numerous.

No SPIROCHAETES seen.

A few yeast cells seen.  
Undigested food + +

No yeast cells seen.  
Undigested food +

In an average field.  
GRAM POSITIVE 10%  
GRAM NEGATIVE 90%

In an average field.  
GRAM POSITIVE 40%  
GRAM NEGATIVE 60%

#### URINE STERILE.

Sp. Gravity	1026	1020
Colour	Straw.	amber
Albumen	none	none
Bile	none	none
Blood	none	none
Sugar	none	none.

#### MICROSCOPIC EXAMINATION of CENTRIFUGED SPECIMEN

R. B. C. one or two  
Pus cells, few.  
Epithelial cells few.  
Bacteria + motile  
No casts seen.

R. B. C. few.  
Pus cells, few.  
Epithelial cells few.  
Bacteria + + motile.  
No casts seen.

#### CULTURE.

N. E.  
Large and small grey  
colonies of B. Coli.

Only colonies of B.  
Coli seen.

#### MICROSCOPIC.

Pure culture of B. Coli.

Pure culture of B.  
Coli.

Details of local, focal and general reactions noted after increasing doses given subcutaneously of a polyvalent B. Coli Stock Vaccine. This vaccine 1 c.c. = 800 million bacilli.

29/6/21  $\frac{1}{2}$  c.c. of the above vaccine was given to C. and to a lad M. who suffered from Myalgia; the injection was given in the arm at 10 a.m. each time, and the results are minutely tabulated below:-

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OBSERVATIONS taken at:-

1 p.m. C. local reaction red size of pea at point of puncture.

M. no local reaction.

4 p.m. C. local reaction, same size.

M. no redness in the skin but a feeling of "tightness".

30/6/21 10 a.m. C. no local reaction.

M. area 4" x 2" red hot and tender to touch.

4 p.m. C. no local reaction.

M. area same size and more tender.

1/7/21 10 a.m. C. no local reaction.

M. size of red patch smaller and less painful.

4 p.m. C. no local reaction.

M. size smaller.

2/7/21 10 a.m. C. no local reaction

M. area disappeared except for a pin point area.

GENERAL REACTION,

C. said he "felt better" after this injection and asked for another, no rise in temperature.

M. said he slept better after this injection, and he did not complain of the local reaction. There was a rise of temperature to 99.2 the first night but nothing to note after this.

FOCAL REACTION

C. there was no decrease in size in the thyroid measurement - no pain nor subjective symptoms in the thyroid.

M. there was no local reaction.

4/7/21 Another  $\frac{1}{2}$  c.c. of the same vaccine was given again at 10 a.m.

To economise space the local reactions were the same, C. showed no local reaction. The focal reaction, the thyroid was slightly smaller, it measured  $17\frac{1}{2}$ ", but this might have been due to the douching, rest in bed and regular diet.

GENERAL REACTION,

C. volunteered the statement that this injection had not done him so much good as the first one.

M. the local reaction was just about the same in size and tenderness. No. focal reaction.

GENERAL REACTION, there was a higher rise in temperature and a slight feeling of malaise.

9/7/21 C. was given 1 c.c., but M. was only given  $\frac{1}{2}$  c.c. as there was a fairly severe local and general reaction.

C./

C. again had no local reaction, focal reaction the thyroid was again  $17\frac{1}{2}$ ", general reaction he felt better after the larger dose.

9/7/21 M. had a larger local reaction and the signs of the general reaction was more severe with a rise of temperature up to 102, he was restless and sleepless, so I did not care to carry on this experimental work on this patient.

As far as C. was concerned, I was unable to carry on my observations for he passed out of my hands but this vaccine treatment was carried on by a confrère, and I have not seen him for months.

#### AGGLUTINATIONS.

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As in the first sterile specimen of urine the culture on Agar was one of pure *Staphylococcus albus*, I tried to find out if there was an agglutination of his blood in the following dilutions, 1/20 1/40, 1/60, 1/80, 1/120, but this was negative.

Later I tried again with *Bacilli Coli*, this was both before and after the injection of the B. *Coli* vaccine, as has been outlined above, the same dilutions 1/20, 1/40, 1/60, 1/80 and 1/120. Both C. and M. were negative, I was surprised for I expected after the larger dose of the polyvalent B. *Coli* vaccine that the test would have been positive.

Mrs S. the female patient was refractory, and I was unable to carry out these bacteriological observations, as a favour I was able to get one sterile/

sterile specimen of urine and one series of wash out. In this examination I found the odour was distinctly offensive, I was unable to find any Spirochaetes, which I found so numerous in C's stools, these Spirochaetes resemble the Spirochaetes of Vincents Angina.

In these observations there are two points which are worthy of notice, and I do not know if the injections of the polyvalent B. Coli vaccine were the cause of these two variations. First C's stools get more offensive after these injections. Secondly the average percentage of Gram Positive and Gram Negative changed, the Gram Negative showing a diminution. I was unable to follow these variations out because of lack of opportunity.

It is strange how often these Spirochaetes are found if a systematic microscopic examination is made of the stools of all patients, similar Spirochaetes are found if microscopic examinations are made of the depositions at the gingival margins of the teeth, so they are not pathognomonic to exophthalmic goitre. I almost apologise for putting in these observations, for there are not enough to be of any clinical value owing to lack of facilities and time, I/

I was unable to carry these to any conclusiveness. But in summarising these observations, there is a similarity seen in the naked eye and bacteriological examination of the faeces of the exophthalmic patient, and of the control, but there are certain points which stand out, the offensiveness of the stools in C. was very marked though he did not have any diarrhoea, and this offensiveness was increased after the injections of B. Coli vaccine. The Spirochaetes mentioned above were striking because they were so numerous. I thoroughly examined C's tonsils and teeth, but could find no signs of active disease nor any spirochaetes.

There is another symptom which I have found only in exophthalmic patients, though I have tried these double enemata on many patients suffering from various diseases. Those suffering from exophthalmic goitre always complained of subjective symptoms such as weakness and lassitude after this treatment, the others do not complain. I have also noticed that the normal act of defaecation makes a patient feel weak and they have to go and lie down to rest after this natural act.

The various theories of the causation of exophthalmic goitre, are,

(1) /

- (1) Intestinal toxæmia.
- (2) Excessive thyroid activity.
- (3) That it is due to a nervous disorder seem to be correct and more or less interwoven. Moreover the ductless glands have been found to participate in the morbid process especially the adrenals and thymus.

The relation of thyroid disease to previous infections has been noticed clinically by many observers, and if the secretion is an important element in the defense against infections, it is not impossible that it is stimulated to overactivity when occasion demands, and if the stimulus be often repeated, it may produce changes which we recognise as pathological. Through the repeated stimulus to overactivity, the gland has become hypertrophied, and its heightened function continues long beyond the stimulus which called it forth. The mechanism against infection depends to a degree on thyroid function. The defensive process that the secretion exerts is by subjecting toxins bacteria etc. to metabolism, precisely as it does in breaking down fats and albumens. So the secretion carries on its protecting role. Indeed PLUMMER of the Mayo Clinic recently stated that the autocoid elaborated in the thyroid is fundamentally a part of the katabolic process of higher human life.

Another/

Another etiological factor which demands elucidation; many cases of exophthalmic goitre are probably due to terror or severe fright particularly when associated with traumatism, also to profound grief, violent rage etc. There is no doubt that fright may alone cause the disease; this has been seen after the air raids in London and after the San Francisco earthquake. CANNON says any high degree of excitement in the nervous system, whether felt as anger, terror, pain, anxiety, grief etc is likely to break over the threshold of the sympathetic division and disturb the functions of all the organs which that division innervates, one of which is the thyroid. They entail also in the light of CRILE'S work, a physical exhaustion of the cerebral nerve cells, the cell bodies of which, show marked chromatolysis. We are evidently dealing with a toxæmia due to impaired metabolism in these cells giving rise to toxic wastes which provoke excessive thyroid activity. Chromatolysis denotes more or less disintegration of certain components of nerve cells their chromatin.

Now excessive mental stress, as fear, anger etc. help on this process and show that nerves fatigued by stimulation, more or less rapidly lose their substance. Briefly put, fright, anger etc. bring about disintegration of the nerve cell by subjecting it to violent stimulation which means excessive metabolic/

metabolic activity. May it not be here that the primary toxin or cause of exophthalmic goitre appears in these cases, e.g. excessive metabolism of nerve cell is known to produce phosphoric acid, cholin and a substance known to be particularly poisonous neurin, a body closely allied to muscarin. So sensitive is the thyroid gland to the latter poison, in fact it was once believed that its one function was to destroy neurin as fast as it was formed. So perhaps in the light of these facts we may learn that a poison though neurogenic, can become the primary cause of the disease.

But why is it that the excessive stress due to fear, rage etc. once terminated and entirely appeased, the morbid process continues? Why do all the morbid symptoms particularly those of nervous origin exist? This is probably due to a vicious circle. The thyroid powerfully stimulated to react against the intoxication itself becomes a destroyer of the nerve cell. This becomes intelligible when we remember that besides the chromatin, the nerve cell is rich in fatty substances, particularly lecithin containing stearic and oleic acids. If we recall the familiar fact that the thyroid gland first attacks fats, breaking them down sooner than/

than any other tissue, we can realise why it is that excessive thyroid activity so actively disturbs the nervous system. Briefly a severe mental stress, rage, fear etc. causes excessive katabolism in the nerve cells and the excretion by them of highly toxic wastes including, neurin, these poisons by provoking a defensive reaction of the thyroid cause it to break down fats, including the fatty components of the nerve cells, thus establishing a vicious circle by perpetuating the katabolism of these cells and the formation of poisons. May not this interpretation suggest a toxic origin of any kind, intestinal, gastric, tonsillar, which would, likewise, entail destructive katabolism of the nerve cells? The only difference probably between this etiological class and the neurogenic, is that in the neurogenic, the sudden emotion or shock to which the nervous system is subjected, at once starts the pathogenic katabolism in the cellular elements. While in the former due to toxins, the morbid process, both as regards the thyroid reaction and pathogenic katabolism in the nerve cells, is started insidiously by the toxaemia, being at first successfully antagonised by the defensive process in which the thyroid takes part. Gradually however/

however, the tidal wave of these toxins rises, the thyroid activity assumes proportions which soon entail not only breaking down of systemic fats, but also of those constituting the ground substance of the nerve cells, thus involving the entire cerebro-spinal and peripheral nervous system.

MORBID/

MORBID ANATOMY and PATHOLOGY.

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On post-mortem examination, general emaciation is usually first to be noted. The prominence of the eyes is seldom so evident as during life, in some cases it is noted that the fat deposited in the orbits is greater in amount than normal.

An increased amount of connective tissue in the neck, enlarged cervical and bronchial glands also swelling of the lymphatic structure of the intestines have sometimes been present. Professor Lorrain SMITH reported a case in which the anterior and peri-bronchial glands showed red and marbled appearances, associated with haemolymph structure. According to KOCHER, swelling of the lymphatic glands in the neighbourhood of the thyroid is a constant feature of severe exophthalmic goitre, the swelling is merely hyperplastic. There is general enlargement of lymphoid tissue throughout the body the tonsils especially are always enlarged.

THYMUS, the constancy of the persistence of this gland and of its hyperplasia in this disease, has been pointed out by many observers. This fact, with the results of thymus treatment, has led to a theory of a thymus participation in the pathology of exophthalmic goitre.

The/

The microscopical appearances of the thymus in this disease, differ in no way from those of the ordinary gland and there is the usual structure, including the corpuscles of Hassall. The persistence of the thymus is difficult to explain, possibly every case in which there is a thymus persisting into adult life, is one of potential or latent exophthalmic goitre.

It has been said that the hypertrophy of the thymus may arise from a vicarious endeavour on the part of the thymus, to make good a deficiency in amount of secretion, elaborated by hypertrophy, but the persistence of the thymus may be explained by the fact, that the victim of exophthalmic goitre is frequently of a lymphatic constitution.

SPLEEN is occasionally enlarged, but shows no histological change, it may be the seat of various accidental degenerations.

HEART - post-mortem the heart usually shows hypertrophy with brown pigmentation and fatty degeneration, especially of the left ventricle and sometimes, though more rarely, in the right ventricle. There is also dilatation and relative insufficiency of the valves. Endocarditis and arteriosclerosis may be associated.

LUNGS/

LUNGS are free from disease, unless they be accidental complications of which pneumonia is the most common.

PARATHYROIDS and PITUITARY changes have been described in these organs but they are neither constant nor characteristic. They are in all probability induced to some extent by the same primal agency which induces the changes in the thyroid and other organs.

MUSCLES. The muscular weakness is striking in this disease, and it is due to a fatty degeneration, atrophy and brown pigmentation of the muscle fibres.

THE SYMPATHETIC NERVOUS SYSTEM, some pathologists have described alterations in this system, but it has not been shown that the changes found, are in any way peculiar to this disease. The late Professor Greenfield described swelling of the ganglia, with marked hyperaemia in the more superficial parts, active invasion of the tissue by leucocytes, and degenerative changes in the ganglion cells, but these may be secondary changes.

CENTRAL NERVOUS SYSTEM - atrophy, degeneration and minute haemorrhage in various parts of the system have been described, but none of them are constant and none of them can be brought into relation with more than a few of the numerous symptoms of the disease.

THYROID/

THYROID usually shows enlargement, cases have been reported in which there is no enlargement. I have never seen such cases, but this I have noticed, that the severer types have very little enlargement, whilst milder cases may be associated with goitre of large size. This is probably due to nutrition, and of individual powers of response to stimuli, the virulence and constancy of action of the exciting agent.

The swelling has a smooth or granular surface, its consistency firm or elastic, it may be tender on pressure and its size can usually be reduced on squeezing. There is increased vascularity, this is not shown post-mortem, but when in the operating theatre, the veins are seen to be greatly engorged and the walls are very friable, the vascularity of the gland, seem to be simply the result of increased activity and will vary according to the stage of the disease. This vascularity is not seen postmortem nor after the gland has been removed, since the vessels collapse, and on section the interior of the gland is rather pale and in appearance not unlike a salivary gland.

Usually the tissue is hard and rather rigid than elastic.

The surface of gland is usually somewhat nodular and rough, there are strands of fibrous tissue which traverse the glandular substance separating it/

it into lobules.

Microscopically there is found the change which appears in experimental compensatory hypertrophy, strands of fibrous tissue run in every direction, separating the tissue into lobular masses, and in these lobules the alveoli are often separated by a fibrous tissue stroma much more abundant than in a normal gland. The alveoli are no longer rounded, full of colloid and lined with a low, cubical epithelium, but are extremely irregular in size and in form.

The hyperplasia of an exophthalmic thyroid differs from the thyroid of a simple goitre in this, that there is much greater degree of lymphocytic infiltration, which occurs, indeed some consider that it is only where lymphoid proliferation is found, that the condition can be considered to be one of true exophthalmic goitre. This feature of the thyroid is in conformity with the generalised lymphatic hyperplasia, and with the lymphocytosis which is present in this disease.

The epithelium becomes columnar, not only in the large alveoli, but also in the smaller ones, it is irregular. The details of the structure of the epithelium can easily be made out, the cells are plump with a finely granular protoplasm and a sharp outline, the free surface is sharply marked. The nuclei/

nuclei lie near the base or near the free end of the cell. Mitotic figures are frequently formed. Desquamation of the epithelium is not uncommon, but may this not be due to the unavoidable handling during the operation for removal?

The colloid varies greatly in different cases, but it is markedly diminished in amount and altered in quality, the normal hyaline material being replaced by a very palely staining substance, or by a ragged, shreddy, granular or vacuolated mass which has no longer the refractive qualities of the normal colloid material.

The iodine content of the gland has been investigated and in cases where the follicles are empty the iodine content is much below that of a normal gland. Sometimes hardly a trace of iodine is to be found, but in cases in which colloid material is present in the follicles, an extraordinary quantity of iodine has been found, as much as 40 or 50 grams in one lobe. The picture is one of an activity secreting, a hypersecreting gland attempting to make up for the greater demands of secretion.

SYMPTOMS/

S Y M P T O M S .

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Few organs or tissue escape injury in this disease, consequently the symptoms which may develop in its course are most diverse.

Thyroid enlargement is palpable, it may be of considerable size, often asymmetrical with the right lobe more prominent than the left. It is smooth of surface and elastic in consistence. It rises with swallowing, a point which is useful in diagnosis. During the course of the disease, the goitre varies in size, the swelling of the gland may temporarily increase after excitement or over-exertion, or at the menstrual period. With a diminution in size of the thyroid, I have usually found a general improvement in the patient's condition, but this is not always the case.

The enlargement rarely causes pressure symptoms, but when the disease is superadded to an old goitre, there may be pressure on the trachea or nerves and the symptoms vary according to the size of the goitre. The vessels are greatly engorged, and the whole organ may pulsate visibly, the pulsation may be transmitted from the carotids, but, as a rule, it arises from pulsation in the vessels of the gland itself. The pulsation is palpable and a thrill may be communicated. On auscultation a bruit systolic in time is usually heard, this bruit is of diagnostic importance/

importance, as it is rarely heard in simple goitres.

There is no necessary relation between the intensity of the symptoms and the size of the gland, and in some most severe forms of the disease, the thyroid enlargement is inconspicuous. The enlargement is one of the so called cardinal symptoms of the disease.

#### CIRCULATORY PHENOMENA.

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These are characteristic and constant features of the disease, patients rarely fail to notice changes in the rate and rhythm of the heart beat, and in many cases palpitation is mentioned as the cardinal symptom. At first palpitation is noticed only after exertion or excitement, and then is important only when it is unusual for that patient. Sometimes it is associated with a feeling of suffocation, or even swelling in the throat. The heart's action is rapid, and this tachycardia is one of the four cardinal symptoms. The result of experimental research points to the symptom as a sign of increased irritability of the sympathetic nerves. An irritation of the nervus accelerans suggests itself in this connection. Experimental systematic hyperthyroidisation almost invariably produces tachycardia, and there is ground for the belief that this acceleration is due to/

to an increased activity of the sympathetic nerves, and is an effect of the increased amount of the thyroid substances circulating in the blood. It is interesting to note that the active principle, thyroxine obtained by KENDALL when given in excess, does not cause tachycardia, if, however, amino-acids are injected simultaneously, the pulse rate is enormously increased. Proof of the hyper-functioning is found in the hypertrophy of cardiac muscle. But tachycardia may, also be due to the sustained dilatation of the arterioles and to increased metabolism.

The rate varies in the slighter cases between 90 and 110 beats in the minute, and in cases of ordinary severity, between 110 and 130. The pulse rate varies in the same individual at different times. A pulse persistently 95, while the patient is under observation in bed, is suggestive of this malady.

Arrhythmia is not uncommon and is often seen in these cases.

Often, after excitement or exertion, the patient exhibits paroxysmal tachycardia, when the pulse runs up to 200 beats per minute, and this is due to the less common condition of extra systoles starting in the auricles. Although this does not strictly constitute irregularity, except when the paroxysms last but a few seconds, it will be convenient/

convenient to consider it here with the condition of arrhythmia to which it is so closely allied. LEWIS describes the features of a simple tachycardia such as occurs in exophthalmic goitre, pulmonary tuberculosis, infective conditions and alcoholism as follows: "the pulse rate falls during rest or recumbency, rising to the original rate on standing up again, it is enhanced by exercise, emotion and the like, the electro-cardiogram is of the normal type and the rapidity is gradual in onset and termination! This simple tachycardia should never in the absence of signs suggest cardiac lesion.

In one of my patients this paroxysmal tachycardia often came on, it was usually started by the lady bending down to pick up anything, such as a pin or some work which she had dropped - her pulse would race along at 180 to 200 to the minute: lying down did not stop it and on one occasion this went on continuously for 19 hours. These attacks are very distressing to the patient and leave her limp and worn out as well as preventing her from sleeping during the night. If the patient has not already been taking digitalis, I have found that one white pill of Nativelle's crystallised digitaline containing  $1/240$  of a grain of crystallised digitaline, given/

given every 4 hours till the tachycardia ceases, is effective, especially if an ice-bag is placed on the praecordium and the patient is kept lying flat on her back with no pillows. Emphasis has to be placed on the necessity of not giving this Nativelle's digitaline if digitalis has been regularly taken before, for once I nearly lost a patient from persistent vomiting, when for three days she was unable to keep anything in her stomach. I have been so situated that I have been unable to get electro-cardiographic tracings of my patient.

The carotids pulsate visibly and this is generally a conspicuous feature of this disease. MUSSET'S symptom is often seen as in aortic incompetence, the nodding of the head synchronous with the throbbing of the carotids.

The heart beat may be perceptible through the clothing, on palpation it can be felt as an unusually violent impact 'pounding' - sometimes there is a systolic thrill or a diastolic shock. With this the apex beat may not be much displaced or even too far out, as in the nipple line, it may be in the 5th or even the 4th interspace - this depends on the severity and duration of the disease. Naturally the more/

more severe and old standing the disease, the greater the hypertrophy and dilatation of the heart. The dulness is increased, especially on the left.

On auscultation the sounds are usually loud, but the 1st sound is rarely clear, and a rapid toneless 1st sound resembling the second sound, is an early and a characteristic sign of hyperthyroidism. The sounds may be audible at a distance.

Murmurs are common, especially at the apex, conducted into the axilla sometimes the same or a different murmur is audible over the base. Diastolic murmurs in the aortic area are sometimes present. These murmurs are all of functional origin, probably muscular insufficiency is the chief factor, anaemia is a rare one. Valvular disease of endocarditic origin is sometimes associated.

The Blood pressure varies in different cases; in some of my cases the systolic pressure is normal, sometimes it is slightly raised, usually it is low in this disease, though in one of my cases it was high - up to 150. The Blood pressure varies according to the state of the heart muscle and the degree of peripheral dilatation so usually the blood pressure in exophthalmic goitre is usually low.

BLOOD/

BLOOD PICTURE - haemoglobin, erythrocytes and total leucocytes are all within normal limits in those cases which are not associated with chlorosis and other forms of anaemia, which are common accompaniments. There is, however, a relative and absolute increase in mononuclear together with a percentage decrease in polymorphonuclear leucocytes. The increase in mononuclears, including both large and small, often amounting to as much as 50 per cent. There is an increase in eosinophiles, sometimes a marked increase, which should direct attention to the intestinal tract for worms. These changes in the Blood Picture are common to exophthalmic goitre, as well as to simple goitre, and myxoedema, and they occur, as is well known, in many other affections notably intoxications and intestinal disorders.

As regards lymphocytosis in connection with thyroid disorders, an Italian physician claims that leucopenia observed in cases of exophthalmic goitre with an increase of mononuclears, is not characteristic of this disease, but is found in almost all abnormal conditions of the thyroid. This condition seems to be due to a reaction on part of the thymus and of the lymphatic system in any form of dysthyroidism, in other words whenever an infective toxæmia/

toxaemia can be excluded in case of lymphocytosis, it is to be considered as an expression of an endocrine toxaemia that is a function variation of the thyroid thymus lymph systems. May not the toxaemia cause both?

Oedema of the lower extremities is not infrequent as a result of cardiac weakness. At an early stage there may be a general oedema which may be one of the main features of the disease, and there may be effusions into the serous cavities as well as anasarca. Sometimes local oedema has been observed affecting the eyelids or affecting one side more than the other, thus independent of position, and is associated with vasomotor disturbances.

Patients suffering from this disease probably die from ventricular fibrillation in the production of which two factors are concerned, one pre-existing myocardial degeneration and high blood pressure.

Dangerous cases are those in which there is definite myocardial degeneration, and in which the blood pressure is high. There is a great difference of opinion as to the usual blood pressure in exophthalmic goitre, but may it not be explained in this way, that it is tri-phasic? First a transient rise, secondly a fall, and, lastly a rise. Haemorrhages sometimes occur from the nose, stomach or the skin.

EYES/

EYES. The protrusion is another cardinal symptom, and was noticed by PARRY in his first case - however, exophthalmos, like other signs is sometimes absent. It comes on comparatively late and varies much in degree from a slight prominence that can only be noticed by those who know the patient well, to a condition where the eyelids cannot voluntarily be closed over the protrusion, nor do they meet in sleep. The degree bears no relation to the size of the goitre, nor to the severity of the other symptoms. In many cases the exophthalmos is unilateral or larger on one side than the other. The protrusion varies greatly at different times in the same individual, at one time especially when the patient is quiet, it may be scarcely noticeable, at another under slight mental excitement it is a prominent feature.

There are various theories as to the cause of this protrusion:-

- (1) Increase of orbital fat, this has been found in some cases at the post-mortem but the rapid protrusion in some cases proves that such a condition is not primary.
- (2) Vascular congestion and oedema have been assumed, this is often present with oedema in the folds between the lids and edges of the orbit.
- (3) Now it is held that the cause is due to the sustained contraction of the levator palpebialis muscle causing contraction of the lids and exposure of the sclera as well as to contraction of the protractor bulbi muscle of Muller which has/

has a sympathetic innervation, causing protrusion of the globe.

Experimental stimulation of the cervical sympathetic will produce exophthalmos; this was proved by CLAUD BERNARD'S classical experiments.

Exophthalmos cannot be produced experimentally in animals by thyroid feeding, nor is exophthalmos peculiar to exophthalmic goitre, besides aneurisms, inflammations and tumours of the orbit, it is sometimes present in cases of atheroma with dilatation of the arteries and in chronic cyanosis of the head, also it is sometimes seen in cases of lead poisoning, as a toxic vasomotor condition.

Various signs are seen in the eyes and are of diagnostic value. STELLWAG'S sign which was first described by DALRYMPLE, an increase in the width of the palpebral fissure, due to retraction of the upper lid, and with this is associated diminished frequency and incompleteness of winking under reflex stimulation, in consequence of the retraction of the lids, the sclerotics show all round the iris. It is due to spasm of the levator palpebrae superioris, and its explanation is generally found in a higher excitation of the nerves. This sign occurs early, is rarely absent and is a very useful diagnostic point. This sign is not peculiar to this disease/

disease, besides it occurs in maniacal conditions, in hysteria, tabes and pregnancy.

VON GRAFE'S sign consists in the lagging of the upper eyelid in downward movements of the eyes, this sign cannot be seen so well in the lower lid, although, if the patient looks up, the jerking of the lid can be seen in that motion. This sign is not always present, and it is not peculiar to this disease, but may be observed in other individuals, and it is possible to produce the sign voluntarily.

MOBINO pointed out another sign, namely, insufficient power of convergence for near objects, on convergence, the patient experiences a sense of strain, but has no double vision. It occurs in many myasthenic conditions. Occasionally some weakness of the external ocular muscles exists, so that there is some slight drooping of both upper eyelids, or some paresis of the external recti, producing double vision on looking at the extreme right or left.

Paralysis of the 3rd nerve and multiple paralysis of the eye muscles have been observed. A glistening slightly oedematous condition of the conjunctivae is seen, - lids are dark and sometimes swollen, - there may be an excessive secretion of tears or abnormal deafness. Tremor of the lids when closed over the bulb may occur. In severe exophthalmos there is often associated pain and subjective tension in the eyes/

eyes. From diminished movement and lessened sensitiveness of the cornea, ulceration is favoured - ulceration is a dangerous occurrence.

No defect of vision, as a rule, accompanies the exophthalmos, but besides the sense of straining which sometimes accompanies efforts at convergence, patients often complain of various subjective symptoms, such as flashes of light, feelings as if the eyes were being pushed forwards, and I had a patient who complained that letters were blurred, especially at night, when the eyes were tired.

A new ocular symptom has been described which is supposed to be characteristic of exophthalmic goitre, but I have not seen sufficient cases, since I came across the description of its pathognomy. After extreme lateral rotation of the eye with fixation on an object at this point maintained for a second or two, on attempting to follow this fixation point, as it is rapidly swung into the median line, one of the eyes fails to follow the other in a complementary manner into proper convergence. An apparent divergent strabismus is momentarily manifest.

On ophthalmoscopic examination, pulsation of the retinal vessels may be seen, this is sometimes /

sometimes limited to the vessels of the disc, but usually it is also visible in its neighbourhood. The retinal vessels are sometimes dilated and tortuous.

NERVOUS SYSTEM always suffers in this disease, and often it is the seat of the earliest symptoms, though rarely the patient may remain placid, good tempered and generally amiable, but this has not been the case in any of my patients. Patients usually complain of nervousness, and this one finds to be mental irritability, emotionalism, excitability and restlessness. The restlessness is not a mere fidgetiness, but as PLUMMER describes it "purposeful restlessness", there is a folding and unfolding of the arms, the legs are crossed and then uncrossed, buttons are buttoned up and then shortly afterwards unbuttoned, the hair is patted here and there, there is always some idea behind the movements. The patient longs for constant change and feels she must be continually seeing or doing something new. The patient varies, at one time she is low spirited and tearful, at another she is "on the heights", buoyant and smiling. She is inclined to be wayward and wilful, resents having her will and desires crossed. She is easily upset by any unusual occurrence, a sudden noise from the exhaust pipe of  
a/

a car or motor cycle, the slamming of a door, the arrival of a telegram may upset her for hours. The intellectual powers may remain unimpaired.

Usually there is insomnia, sleep is often disturbed and troubled with dreams. There is often intolerance of the company of strangers, in one case of mine, the patient a married woman could not bear the company even of her husband though they were on the most affectionate terms.

Some patients are apt to become suspicious, untruthful and all are discontented. There may be more severe mental disturbances, and this is a point to be remembered in prognosis, for if there are serious mental symptoms, the case is usually fatal, there is a confusion of ideas, hallucinations visual or auditory, deliriums of persecution, of grandeur occur, also suicidal and homicidal mania - fortunately these are not common. Headache is a common symptom and it is generally not localised.

Patients suffering from exophthalmic goitre are liable to neuralgia which may occur in any part of the body, these, especially the facial, are troublesome and obstinate symptoms. Local twitchings are often annoying also cramp which seems to especially affect the legs at night.

Signs/

Signs of increased activity of the sympathetic nervous system are to be found in the greater vasomotor excitability, the increased secretion of the sweat glands, the tendency to heightened temperature, and the increased production of heat. The increased amount of adrenalin in the blood points to the same conclusion. The serum of the blood of patients suffering from this disease causes the pupil of an enucleated frog's eye to dilate.

**MUSCLES.** Tremor is a characteristic symptom and it varies from a fine, barely perceptible tremor up to a distinct shaking of the extremities, head or even of the whole body. I saw a patient whose father told me she shook the room when she even lay down on her bed. These tremors are best seen when the hands are stretched out and the fingers extended, a good way to record the tremor is to make the patient draw a line slowly in a measured time. These tremors are best appreciated by touch - they are rapid and rhythmic 8 to 10 to the second.

As one would expect the tremor is more obvious if the patient is flurried, such as in the presence of strangers, or on the arrival of the physician/

physician, and they are more conspicuous when the patient is standing than when she is lying down.

The writing is usually affected and delicate movements such as fine sewing etc. are interfered with.

Muscular weakness is noticeable, the patient often volunteers the information that she easily gets tired, it is a painful effort to go upstairs, a useful diagnostic sign is this, that she finds it impossible to step on to a chair or a distance 18 inches from the ground.

Fatty degeneration and atrophy of the muscle fibres with loss of the normal striation has been found in various muscles.

**SKIN.** Numerous cutaneous complications differentiated into vaso-motor, motor-trophic, toxic and microbic are seen in exophthalmic goitre. To the first division, belong flushing oedema and purpura. Among trophic manifestations are melanoderma, seldom vitiligo and scleroderma and alopecia. Toxic erythema especially urticaria, ferunculosis, pyodermatitis, eczema and puritis belong.

There is a flushing of the regions of the head and neck especially when the patients think they are being looked at, or under excitement. The skin is usually warm and moist. This increased moisture of /

of the skin causes a diminution of the electrical resistance, and dryness of the skin is suggestive of the antithesis namely myxoedema. The warm skin is usually associated with a feeling of subjective warmth, and a tendency to feel better in cold weather. Patients who used to suffer from chilblains now suffer from them no more. Hot weather is oppressive, less clothes are used both by day and by night. In 92 per cent of cases of hyperthyroidism, rubbing of the skin lightly in the region of the thyroid with the finger, produces a very red flush, much brighter red than could be elicited by rubbing the skin elsewhere. This is a pathognomonic sign. Various degrees of vasomotor anomaly are shown by rubbing or scratching the skin up to the striking and even lasting dermographism and urticaria. The itching of the skin is often a troublesome symptom, it is presumed to be a toxic symptom due to the thyroid secretion, as it has been experimentally produced by feeding with thyroid.

Pigmentary changes are often seen, the complexion suffers and the skin becomes sallow. There may be bronzing of the skin in ADDISON'S disease, but more often I have seen patches of irregular discolouration on various parts of the body, where /

where pigment is present or where pressure is exerted, the parts usually affected are the flexures of the arms and thighs, the nipples, the abdomen, lumbar region, face, the neck and the back.

Scleroderma has often been observed. I have a patient now under my care who is suffering from alopecia. Her nails become brittle and show atrophic changes. The teeth usually become carious and need frequent attention from the dental surgeon. The nutrition of the hair suffers, the hair thins and falls out, also I have seen complete disappearance of the hair in the axilla in the female patient

**LYMPHATIC SYSTEM** . Often at operation for thyroidectomy the hyperplasia of the lymphatic glands near the thyroid are found, in some cases this hyperplasia is also found in other regions, such as cervical, axillary and inguinal. There is certainly a hyperplasia of all the lymphoid tissue seen in all exophthalmics.

**RESPIRATORY SYSTEM** . Respiratory rhythm is increased, due in part to nervous irritation and possibly also to the action of toxins produced in the thyroid gland and to increased metabolism. As a result of muscular weakness of the muscles of the chest wall, and of cardiac weakness, the patient is apt /

apt to suffer from shortness of breath on exertion, or when under excitement. Rarely serious attacks of dyspnoea come on, but some cases have died during these attacks.

A dry cough is often troublesome and is no doubt nervous in origin.

**ALIMENTARY CANAL.** The appetite is always good, and often capricious, but in spite of the voracious appetite the patient remains thin. However if the disease is progressing unfavourably there may be more or less complete anorexia.

Thirst is usually complained of, the increased metabolism accounts for the abnormal appetite and the excessive perspiration explains the reason for the thirst.

Vomiting apparently unrelated to the taking of food is not uncommon, and I had a case in which it was a very grave symptom, the patient complained of epigastric pain and was unable to retain anything in her stomach - even vomiting up the water which was swallowed from the melting of the ice in her mouth. There was intense prostration, restlessness, some dyspnoea; fortunately the symptoms after three days passed off, but these cases often end in death.

As a rule there is hypoacidity of the gastric/

gastric contents in this malady, and indigestion is often a distressing and a very troublesome symptom to relieve - careful dieting and doses of bismuth I have found most effective.

Diarrhoea is a very common symptom, and is often the earliest one noticed. Occurring in 50% of the cases, it comes on usually without any special cause, and is rarely attended with any pain or griping. The stools are usually very offensive, and may be coloured with bile, though I have noticed usually that bile colouring is deficient, showing poor digestion of the food, and makes one think of some toxic cause of exophthalmic goitre; some go so far as to say that 50 per cent are due to intestinal toxemia. Also this diarrhoea stops suddenly.

I have noticed that the giving of enemata also that even the normal act of defaecation makes the patient feel weak, and have to go and lie down after an evacuation. RONTGEN says that bismuth meals should be part of the routine treatment in the examination of all cases of exophthalmic goitre.

THE KIDNEYS are rarely affected, though albuminuria with hyaline casts is usually present when the heart is affected and there is dilatation. This albuminuria is not a constant nor a common feature of the malady. I noticed in a few cases where/

where I have been able to make observations, that if the urine is put up into glass jars and left for a short time, the urine becomes turbid, and under the microscope numerous motile bacteria, probably B. Coli are seen moving in the field - however it is not pathognomonic in exophthalmic goitre, for I have found it in other cases chiefly intestinal toxæmia. It is remarkable how common bacilluria is, if one cares to examine the urine. In some cases there may be acetone in the urine and it is a grave symptom. I have had several cases who suffered from polyuria, this it may be explained, is caused by the greater drinking of water and large meals, in other cases it may be of nervous origin.

Glycosuria has been observed, and lately much work has been done on the causation of this symptom. Thyroid extract given internally, is known to excite glycosuria, this has been noticed when small doses are given to improve the circulation, cure obesity etc. In exophthalmic goitre, there is a lowered tolerance for sugar and sometimes a definite glycosuria, while in the antithesis, myxœdema, there is an extraordinary increase in sugar tolerance, which is reduced by thyroid administration. The glycosuria is distinct from lactosuria of pregnancy, which is probably due to the stimulating/

stimulating effect of pregnancy on the thyroid and the pituitary.

Adrenal glycosuria, although there is experimental evidence that glycosuria can be excited by an excess of adrenalin, there is very little clinical evidence of a definite adrenal diabetes. Emotional temporary glycosuria is naturally regarded as due to excessive adrenal stimulation through the sympathetic, and cases of slight temporary glycosuria in soldiers suffering from shell shock are probably of this class.

We may conclude that the underaction of the pancreas or the overaction of the adrenals, thyroid, pituitary can all lead to glycosuria. How is such a loss of balance supposed to be brought about if there is no evidence of disease in any one gland? I should like to call attention to the way in which the balance could be brought about by the sympathetic. The following general statement may be said to have gone beyond the state of hypothesis to that of well nigh established fact.

1. Sympathetic stimulation increases blood sugar as a defensive measure.
2. Sympathetic stimulation causes increased secretion of the thyroid, adrenals and pituitary.

3./

3. Vague stimulation excites secretion of the pancreas, and on the generalisation of the opposing actions of the para-sympathetic and sympathetic, it would appear probable that sympathetic stimulation inhibits the secretion of the pancreas. The antagonism between its internal and external does not mean an antagonistic nervous supply, it means a diversion of nervous energy from one channel to another.
4. The general effect of sympathetic stimulation is katabolic and mobilisation of blood sugar is a preparation for katabolic action.
5. Therefore the sympathetic, both by increasing the secretion of the glands, which diminish carbohydrate tolerance, and by inhibiting the gland which increases carbohydrate tolerance, would raise blood sugar above the leak point and glycosuria would result. It is said that the failure of the carbohydrate of the food to be assimilated owing to the defective action of the internal pancreatic secretion, would produce far more profound disturbance of metabolism than the increased action of glands, which simply increase the sugar mobilisation because the action of the latter would be limited to that on the stored carbohydrate in the body, which does not reach a high amount. This accords with the fact that pituitary and thyroid glycosuria are more amenable than the glycosuria dependent on a finite pancreatic disease.

Diabetes is associated with neuropathic family history, with exophthalmic goitre, with excitement, shock and bereavement, and has been recognised for many years.

If exophthalmic goitre is a state of "continuous fear", diabetes is a state of "continuous mobilisation of the blood sugar, and both of these/

these may be due to dissociation of the sympathetic nervous system. The evil effects of depressing emotions, of anxiety, fear, pain and anger, receive an explanation, when we see that through the sympathetic nervous system they can lead even to structural change. Designed as an intensive preparation for action or defence, the sympathetic response may be so dissociated, perverted or prolonged, as to produce through the thyroid gland, exophthalmic goitre, with its danger to life. Through the pituitary body, diabetes insipidus, with its attendant discomforts; through the pancreas and other endocrine glands, of excessive mobilisation of the blood sugar, which is the first stage of the metabolic disorder, culminates in diabetes, it may disorganise digestion by exciting spasm and atony in stomach and bowels, and inhibiting the secretion of gastric juices, - it may keep blood pressure at a level which is inappropriate for the task of the heart and arteries. These efforts are not necessarily distinct, thus intestinal stasis from sympathetic inhibition, causes toxins of putrifactive origin to be absorbed, which in their turn lead to vaso-constriction and hence an unduly raised blood pressure.

SEXUAL ORGANS: Excessive thyroid secretion may affect/

affect the genital functions in two ways.

1. May stimulate them to excessive activity.
2. The general metabolism may be so upset that the genital function ceases.

There is no doubt that there is a condition of hyperthyroidism which produces excessive menstruation, and which is totally unassociated with any symptoms of exophthalmic goitre. This condition is usually seen in girls about puberty, usually just before or after menstruation begins. It may be that excessive activity is due to incomplete functional development of ovaries, but whatever the cause, there is not infrequently menorrhagia. I have seen the same enlargement in amenorrhoea.

It is usually stated that in this disease menorrhoea exists. I have not been able to satisfy myself that this is so, until metabolism has been seriously disordered, and the increased quantity of calcium, which is excreted by way of the urine and faeces - a constant phenomena in exophthalmic goitre, is so large, that there is no excess for the ovaries to excrete in the menstrual flow.

Usually in the early stages of the disease there is menorrhagia. Should a large body of evidence eventually disprove this view, it will be a positive/

positive argument of great value that in exophthalmic goitre the secretion is perverted even if there be also an excess of the normal. But in this matter also, we must remain in comparative ignorance until our knowledge of the pathology of this disease is more definite. HELEN GURNEY found amenorrhoea in 15 per cent of cases analysed, but did not state what stage of the disease the patients were at. The effect of menstruation in exophthalmic goitre is not constant, sometimes the goitre diminishes in size and sometimes increases in size.

Probable excess of thyroid secretion except in very advanced cases does not interfere with fertility. It would be strange if it did, for we know that there is an increase in thyroid activity during the early months of pregnancy and possibly throughout, but it is no less a fact that women with marked exophthalmic goitre rarely become pregnant, and if they do, the disease is aggravated. Often there is haemorrhage after delivery, often severe post-partum haemorrhage. These women should be given large doses of calcium citrate if they become pregnant, for there is an excessive excretion of lime/

lime salts in this disease. Pituitary extract should always be injected after labour in order that its direct action on the musculature of the uterus bleeding may be prevented.

The sexual organs do not as a rule show prominent change. Loss of sexual power occasionally occurs in male patients. Menstruation is usually in proportion to the condition of the blood and nutrition. There may be atrophy of the uterus and ovaries, but this is rare. The mammary glands are usually more or less atrophic, though sometimes they seem to get large during this disease; this may be related to a lipomatosis sometimes seen in other parts of the body.

Pelvic and sexual disturbances apart from disorders of menstruation above mentioned are often associated with this malady. In married women I have met with sexual incompatibility with their husbands.

**EPISTAXIS.** I have a case where epistaxis is a prominent feature - others have recorded pulmonary, intestinal, meningeal and cerebral haemorrhages, but I have never seen a case showing any of these, but my clinical experience is not as large as those who write books.

**EMACIATION /**

EMACIATION is an almost constant and a suggestive sign, it is always seen in the post-mortem room. I have a patient under my care who dropped from 11 stones 3 lbs. to 7 stones in weight, and as it happened in this case, those cases which start with diarrhoea with superadded vomiting are the cases which lose weight most rapidly.

This wasting is not from a diminished intake of food, for all the patients eat well though at times their appetites may be capricious.

FEVER. There is a subjective feeling of warmth or even heat, but a temperature is rare except in fatal cases. It is probable that pyrexia when present, is due to some complication. This subjective feeling of warmth necessitates the patient sleeping in a bed by herself, for even in the coldest weather she only uses a very small amount of clothes, and she always prefers cold weather, and is intolerant of heat.

METABOLISM. My attention was first drawn to the changes in metabolism and the method of recording the metabolic rate, when I visited the Mayo Clinic in February 1920. Thanks to the kindness of the physicians there, I saw everything and I have no doubt in /

in saying that the basal metabolic rate, as it has been worked out by Drs PLUMMER and BOOTHBY, and the study of the metabolic changes, are of the utmost importance and are a great help in an accurate diagnosis of those border line cases of exophthalmic goitre which are so difficult to diagnose. In each animal there is a basal metabolism. By "basal metabolism" or better "basal metabolic rate" of an organism, is meant the minimal heat production of that organism measured twelve hours after the ingestion of food and with the organism at complete muscular rest. This minimal heat production may be determined directly by actual measurements by means of a calorimeter or indirectly by calculating the heat production from an analysis of the end products which result from oxidation within the organism, or specifically from the amount of oxygen used and the corresponding amount of carbon dioxide produced, together with the total nitrogen eliminated in the urine by the sweat glands etc. although for clinical work the nitrogen of these excretions may be neglected.

Life processes are those of oxidation with the elimination of heat. Technically it was necessary/

necessary not only to measure the amount of heat lost by radiation and conduction from the body, but also to collect accurately the various end products resulting from combustion within the body, from which data the heat production can be calculated in order to prove, from a comparison of the results obtained from the two methods, that the law of conservation of energy also holds for the living organism. Also the heat values of carbohydrates, fats, proteins had also to be determined in order to calculate the heat derived from their combustion in the body. The method - a mask is adjusted over the patient's mouth and nose, and by means of expiratory and inspiratory values, the total volume of the patient's expired air is collected in a gasometer for a known period of approximately ten minutes. Duplicate determinations are made of the carbon dioxide and oxygen content of the expired air, the analysis being done in the Haldane gas analysis apparatus. Since the ventilation rate for each minute is known as well as the amount of carbon dioxide produced, and the oxygen absorbed, it is possible to calculate by means of caloric tables, the total number of calories produced each hour.

The/

The following points in the routine determination of the basal metabolic rate deserve discussion. To obtain comparable results, the patient must be in the post-absorptive condition, that is, he must fast for at least 12 hours preceding the test. It is very important that this rule must be observed because all kinds of food cause an increase in the heat production, and this effect may not entirely disappear for 12 hours after the ingestion. Moreover, the patient must be in complete rest, and the efforts of previous muscular exertion eliminated by requiring him to rest in bed for 20 minutes before the test is started, for it has been shown in a series of experiments that a rest period of this length of time is quite sufficient to obtain the true basal metabolism. During the preliminary test period, an observer sits with the patient noting at intervals the character and rate of the heart beat and the respiration. Likewise about the middle of the period the blood pressure both systolic and diastolic are obtained. After 20 minutes rest, a mask is accurately adjusted over the nose and mouth of the patient and securely held in place by means of tapes so that there is no leakage of air round the mask. A mask is preferable to either a mouth piece or nasal tubes. During the test proper, the observer sits with the patient/

patient, recording the pulse and respiration rates and noting and recording on a special chart any movements. Care is taken to impress on the patients that even slight movements materially affect the test, and it is almost always possible to obtain their complete co-operation. Sometimes, however, in an extremely nervous patient, a basal rate cannot be obtained on the first test. Instead of repeating the test again on the same day, the patient is instructed to return the following morning for a second test. In such instances the rate will occasionally fall to 10 points lower than that obtained the first time, when the patient was unduly nervous and frightened about an unknown procedure. The total volume of the expired air is collected in a gasometer over a known length of time, samples of expired air are then collected over mercury in sampling tubes and analysed in duplicate for carbon dioxide and oxygen. Approximately 10 c.c. of expired air are transferred into the burette of the HALDANE gas analysis apparatus, & after adjusting certain levels a reading of the initial volume of the sample is made, reading to the nearest .0001 c.c. The sample gas is then passed back and forwards/

forwards over a solution of dilute potash to absorb the carbon dioxide. The levels are again adjusted, and a second reading of the volume of the remaining gas in the burette is made. The contraction in volume of the gas due to the absorption of the carbon dioxide by the potash solution divided by the original volume, give the percentage of carbon dioxide in the expired air. In like manner the percentage of the oxygen is determined, potassium pyrogallate solution being used to absorb the oxygen.

The readings should always be checked by a second assistant, to rule out all error. The calculation of the basal metabolic rate from the experimental data is very simple. Knowing the volume of air expired by the patient in a minute (the ventilation rate) and the percentage of carbon dioxide and oxygen in the expired air, it is possible to calculate the volume of oxygen absorbed by the patient in one hour, as well as the corresponding amount of carbon dioxide produced. Since the respiratory quotient, that is the ratio between the volume of carbon dioxide produced and the volume of oxygen absorbed, indicate the kind of food being burned at the time of the determination, and since by the means of caloric tables the calorific value of /

of one volume of oxygen absorbed in the body in the burning of these substances is known, the total heat production in each hour can be readily calculated. The total number of calories must be divided by the surface area, a factor dependent on the patient's height and weight. The number of calories for each square metre of body surface each hour, must then be compared, the normal standard of comparison being dependent on the age and sex of the patient. For convenience, the basal metabolic rate is expressed in percentage of the normal, and when the heat production is greater than the normal, the percentage is plus, and when less than normal the percentage is minus.

The basal metabolic rate is of greatest value in thyroid disorders, because it gives a very accurate mathematical index to the degree of the functional activity of the gland. For example in exophthalmic goitre, the metabolic rate may rise well above 100 per cent, whilst in myxoedema, with apparently complete cessation of thyroid activity, the rate falls to the region of 40 per cent below normal. In milder cases of both groups, the metabolic rate variations from the normal are proportionately smaller. On the other hand, besides thyroid/

thyroid disorders, there are no other diseases that have so far shown to have a constant and distinct variation from the normal in basal metabolic rate, except disorders of the pituitary gland, and in conditions of profound inanition and fever.

Special interest attaches to changes in metabolism in exophthalmic goitre, in simple goitre the metabolism is in no way different to normal, and it is affected by the giving of thyroid extract in a manner precisely similar to that of other persons with normal thyroids. In exophthalmic goitre, on the other hand, the metabolic changes are so characteristic of the condition, that they constitute important diagnostic criteria; metabolism of this disease is characterised by increased expenditure of energy. The respiratory interchange of gases shows an increase of 50 per cent, and over 70 or 80 per cent in the amount of oxygen consumed. The increased consumption, the increased and remarkably fluctuating caloric production, is partly the result of augmented cardiac and respiratory activity, and to an ever increasing degree is due to the nervous excitement and motor unrest, more particularly the tremor. But after making due allowance/

allowance for the operation of these factors, it will be found that in complete muscular repose there is still a large increase in the inter-change of gases. When we remember the effect of thyroid extract on metabolism, it seems obvious that this augmentation is only to be accounted for by a hypersecretion of the thyroid gland. The enormously increased metabolism accounts for the emaciation which is often very extreme. The increased caloric explains the subjective sensation of heat, the profuse outbreaks of perspiration and the tendency, commented on by CHARCOT, to a heightened temperature. That the increased caloric does not produce hyperpyrexia or even fever, is probably due to an adequate degree of activity on the part of the apparatus which regulates heat production. The rise in temperature which occurs shortly before death is probably due to the failure on the part of this apparatus. The increased production of heat is frequently associated with an augmented demand for, and consumption of, albumin, together with a negative nitrogen balance, though the latter is not invariable. The metabolism of nitrogen varies with the fluctuating course of the disease, and may, for longer/

longer or shorter periods, approximate to the normal. The albumin losses and the toxic decomposition of albumin may be counteracted, even when the disease is at its height, by a diet containing albumin or a diet containing carbohydrates, but free from nitrogen. The fats also undergo decomposition. In connection with the metabolism of the carbohydrates, it must be borne in mind that the assimilation of carbohydrates is reduced in exophthalmic goitre and that for this reason an alimentary glycosuria is easily provoked. The feature which characterises metabolism in exophthalmic goitre, is the increase in the total amount of oxidation. An increased metabolism of mineral salts has not as yet been proved, though an increase in the excretion of phosphorus has been substantiated.

No definite instances of increased basal metabolic rate has been found in that group of cases known as neurasthenia or chronic nervous exhaustion. The basal metabolic rate has therefore proved to be of great value in the differential diagnosis of neuroses simulating hyperthyroidism and true hyperthyroidism, and hence it is of the utmost use in diagnosis. It has been noticed that there is a relation/

relation between the pulse and the basal metabolic rate. If the pulse is beating fast, the basal metabolic rate is high, and the converse is also true.

THERE are SOME LITTLE SIGNS of THYROID DISTURBANCE - persistent constipation in infancy and childhood, after all causes have been investigated, will be found to yield to small doses of thyroid extract. When feeding dogs with thyroid through an intestinal fistula, it was found that the intestinal secretion greatly increased and undoubtedly the neuromuscular centres in the intestinal tract produced a more powerful peristalsis. Enuresis in children is also curable, by giving small doses of thyroid - it is a suggestive fact that this trouble is so intractable in girls, and that exophthalmic goitre is more frequent in the female sex. I have not been able to trace any patient suffering from this trouble from youth up to adolescence, to follow out this observation. Epistaxis in childhood too, is a symptom which has to be watched, and can also be cured by small doses of thyroid.

VARIETIES/

VARIETIES of the DISEASE.

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There are many classifications of exophthalmic goitre, and some are apt to be misleading, such as primary and secondary, the latter it must be understood, is when the symptoms occur in one who previously had a goitre, the former, when the goitre develops with or after some other symptom.

KOCHER'S classification, vascular, Basadowised goitre, Basadowian goitre and true Basadow's disease according to the clinical and anatomical standpoint is rather complex, for after all the differences are but gradual and not hard and fast. Complete or incomplete, the latter is the formes frustes of the older writers; this classification is misleading as it depends on the deficiency of one of the cardinal symptoms. Acute or chronic, this classification depends on the duration of the disease, and is not of much value.

Personally the classifications I have found to be the most useful are the following.

1. The VASCULAR TYPE most commonly seen in young women. The thyroid is large and there is much pulsation, rapid pulse, well marked exophthalmos, high basal metabolic rate. The chief complaint is dyspnoea and palpitations, there are nervous symptoms present, but they are not the chief factors of the disease.

2./

2. The NERVOUS TYPE, generally seen later in life than the vascular type and most commonly seen in women at or about the menopause. The thyroid often is but little enlarged. Cardiac symptoms and exophthalmos are present, but not so marked. The chief trouble centres round the nervous system, distinctly nervous often with erratic movements, so that the patient can hardly sit still, she looks as if she had chorea. The prognosis is less satisfactory, for this type of patient is very apt to get mental symptoms.

3. HYPERTHYROIDISM with ADENOMA. This is not true exophthalmic goitre, and is mentioned as a contrast - there are localised soft adenomata, the patient does not suffer from exophthalmos, and this is of great diagnostic value, the basal metabolic rate is not raised.

#### COURSE of the DISEASE.

This is very variable, it may begin abruptly after some emotional strain, shock or injury. However usually it begins more gradually in persons who have enjoyed good health. The symptoms may appear and suddenly disappear, only to reappear with greater intensity later. There are distinct waves of hyperthyroidism with periodic variations, these exacerbations always follow any excitement such as moving the patient to a hospital or a nursing home, aggravated by worry or any anxiety, or shock or at the menopause/

menopause. Also the symptoms are more marked at the menstrual periods, they are aggravated by attacks of acute illness, "colds", influenza and by physical fatigue. These exacerbations subside when the cause for their appearance is removed, but the patient is always left in a worse state than she was before they came on. Looking at a long series of cases, the height of intoxication seems to be produced usually during the first year. Towards the close of the second year, one third of the cases have sufficiently recovered to be able to continue their normal occupation. Others improve at a later date and probably 60 or 70 per cent spontaneously recover after a period of 5 years - the two major factors in non-operative treatment are rest and time.

In the greater proportion of cases, the patients can attend to their household duties, though their existence is pitiable for they are so easily tired and their nervous system is taxed to its utmost. It sometimes happens that the symptoms after lasting for a few months, or it may be for years, suddenly disappear, and this is specially true if the patient can rest not only in the physical but also in the physiological sense. There may be/

be, however, some reminder of the disease left behind for instance, where the exophthalmos is concerned, the spasm of MULLER'S muscle, if kept up for a long period, a contracture ensues giving rise to proptosis and the muscle itself would push the eye out, also secondarily, oedema induced, the orbital tissue by the contracted muscle causes a further proptosis. Also the thyroid remains enlarged after the cure, or some stigmata of nervousness or some uncertainty of temper is left behind.

Relapses occur in some cases after apparent recovery, whether brought about spontaneously or by rest or by surgical means. The symptoms may reappear following some acute illness, severe accident or shock - relapses are not uncommon. When I was at the Mayo Clinic last year, I was told of several patients who had been operated on three times by thyroidectomy the surgeon said this was due to the fact that not sufficient thyroid tissue had been taken away at the earlier operations, but could this not be due to hypertrophy of the remaining glandular tissue? This possibility of relapse should be taken into consideration in making a prognosis.

A/

A SEQUEL of exophthalmic goitre which has been observed in a good number of un-operated cases is myxoedema, and this sequel should be more frequently seen, now that it is the fashion to remove haphazard a large portion of thyroid tissue for the cure of this disease.

DEATH may terminate the malady as its direct action or from intercurrent disease. The cause of death in direct cases is cardiac and nervous exhaustion or from persistent vomiting, from great emaciation, exhaustion following persistent diarrhoea, from dyspnoea, or acute mania. In about 50 per cent of the fatal cases, the end comes from intercurrent disease, the commonest of which are cardiac disease, pneumonia, bronchitis or tuberculosis. The disease itself may prove fatal at any stage. Death may occur within a few weeks of the onset or after the disease had lasted for many years.

The report of the Registrar General gives about 400 deaths annually, and 25 per cent of cases die sooner or later from this disease.

PROGNOSIS. A guarded prognosis should always be given, for the course, duration and the end of the/

the disease in any individual is uncertain. Also so much depends, in each individual case, on the duration of the disease, on the state of nutrition of the body, the amount of rest that can be taken, the class of society to which the patient belongs because, naturally patients in the leisured classes have the better chance of cure.

Relapses often occur after apparent cure. The severer the symptoms, the greater will be the anxiety as to the issue. Progressive emaciation, much prostration, increased and continued rapidity of the heart's action, anorexia, continued vomiting, gastro-intestinal disturbances, icterus and evidences of derangement of the liver are all symptoms which cause great anxiety.

KOCHER thinks lymphocytosis with a decrease in polymorphonuclear cells are an index of the gravity of the disease. Continued fever, mental symptoms and severe cardiac trouble all end fatally. The basal metabolic rate showing the metabolic disturbance in each individual case, is of the greatest importance and is at present the best guide as to prognosis, the higher the increase is above normal, the more severe the case and the worse the prognosis. With/

With rest and ordinary medical attention, one may reasonably expect at least 50 per cent of all cases will eventually recover to the extent of being able to fulfil their daily duties more or less efficiently.

**DIAGNOSIS.** When the cardinal symptoms, enlargement of the thyroid, exophthalmos, tachycardia, and tremor are present, there is no difficulty in making a diagnosis. The presence of a goitre with tachycardia alone, or tremor alone, is not sufficient for the diagnosis of exophthalmic goitre - a thorough routine examination of all the organs of the body, especially paying attention to any sympathetic and metabolic disorders should be made in every case. Neither the thyroid enlargement nor the exophthalmos are essential symptoms. All cases of tachycardia should be carefully examined for thyroid enlargement and ocular symptoms, and if these are absent and the basal metabolic rate is not increased exophthalmic goitre can be ruled out. Too often slight tachycardia with mild nervous symptoms are overlooked to the detriment of the patient, for early rest is essential in the cure, and the earlier the diagnosis is made the better is the prognosis. Exophthalmos is not absolutely characteristic of this disease, for it is seen in cases of orbital tumour /

tumour or aneurism of the orbital artery.

Mild cases of exophthalmic goitre may be confused with neurasthenia, but a careful systematic examination with the reading of the basal metabolic rate, should distinguish between the two conditions. There are certain psychoneurotic persons who have tremor, tachycardia, and an enlarged thyroid, whose type of case is often mistaken for exophthalmic goitre, but here the basal metabolic rate is normal.

Iodism can be recognised by the history, and like hyperthyroidism it gives a positive with GOETSCH'S epinephrin hyper-sensitive test, however it is well to see that a so called case of iodism is not an early case of exophthalmic goitre. Early cases of tuberculosis sometimes have exophthalmic symptoms, and care has to be taken in the diagnosis.

Of late, and especially in America an entity is described which has to be diagnosed from exophthalmic goitre. In exophthalmic goitre, the thyroid secretion damages chiefly the nervous system, and the circulatory system, and produces exophthalmos, but the clinical is dominated by the nervous/

nervous symptoms, although in individual cases the circulatory symptoms or the element producing exophthalmos may seem to be in excess. The intoxications from toxic non-hyperplastic goitre may be divided into two emerging groups,

1. In which the cardiac toxin predominates, in which the clinical pictures closely resemble, and in many instances cannot be differentiated from the cardio-vascular complex resulting from alcoholic syphilitic septic and other well known toxins.
2. A group more closely approaching the picture of exophthalmic goitre and including cases which they say have been erroneously so diagnosed by many. In this group are the cases in which there is a degeneration of encapsuled adenomata. While they do not have exophthalmos, in lieu of this they may have the staring and widening of the palpebral fissure. The pulse is irregular in tension and rhythm. Circulatory changes and muscular weakness are marked.

The average lapse of time between the appearance of non-hyperplastic goitre and toxic symptoms is 14.5 years, that the patient comes under observation 3 years later indicates that the onset is usually insidious. Nervousness, tremor and loss of strength and weight as a rule develop slowly, but may appear suddenly long before definite evidence of myocardial damage. In some cases the clinical aspect as noted above, closely approaches that of exophthalmic goitre, however the symptoms are less complex/

complex, less definitely associated and except for a damaged heart less intense. There is much evidence to suggest that during the 14.5 years previous to the onset of definite toxic symptoms many of the cases of non-hyperplastic thyroid may develop arterio-sclerosis, in many cases showing the combined picture of thyrotoxicosis and arterio-sclerosis. The development of a typical syndrome of exophthalmic goitre in a case having a definite history of simple goitre, means that the hyperplastic goitre has been super-imposed upon the simple type. The onset of exophthalmic goitre, is as a rule, relatively acute and the course of the disease fairly definite, the clinical picture early in the history, is that of a toxin acting directly on the more vital organs, more notably on the central nervous system and vascular system. Later it is made more complex by the interactions of those organs whose function has been directly disturbed by a toxin. The order of onset of the most important symptoms is as follows..

- 
1. Cerebral stimulation.
  2. Vasomotor disturbance of the skin.
  3. Tremor.
  4. Mental irritability.
  - 5./

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5. Tachycardia.
  6. Loss of strength.
  7. Cardiac in-sufficiency.
  8. Exophthalmos.
  9. Diarrhoea.
  10. Vomiting.
  11. Mental depression.
  12. Jaundice and
  13. Death.
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The Mayo Clinic taking a large number of cases have worked out this differential diagnosis between toxic adenoma with hyperthyroidism and exophthalmic goitre.

#### TOXIC GOITRE.

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- |   |                                       |
|---|---------------------------------------|
| 1. Average age 36.5   | exophthalmic goitre<br>average age 22 |
| 2. Enlargement came on<br>on 5 to 10<br>years earlier.                        |                                       |
| 3. Time elapsing between<br>appearance<br>of goitre and<br>onset of symptoms. |                                       |
| 14.5 years  | 9/10 of a year                        |
| 4. Exophthalmos<br>usually absent   | almost always present.                |
| 5. High Blood<br>pressure.  | Blood pressure varies<br>often low.   |
- 

This/

This type of toxic goitre is quite as dangerous if not more so than exophthalmic goitre because the toxin seems to have a selective action on the heart, the so-called thyrotoxic heart. This type is likely to be overlooked because there are no symptoms of exophthalmos. Many simple adenomas are proved to degenerate and produce toxic symptoms. An atoxic goitre may be of long duration before producing toxic symptoms. There is a danger of administering iodine in case of goitre of long standing, it may set up toxic and sometimes fatal symptoms. Toxic goitre is not definitely improved by ligation of the superior thyroid arteries.

Exophthalmic goitre may be super-imposed upon any form of goitre, hypertrophic, colloid, adenomatous or cystic but a vascular and probably painful enlargement of the thyroid is much the most common.

There are certain definite signs which though not characteristic of the disease itself, yet taken in combination, help us to make the Diagnosis certain, I am not here speaking of the typical case with well marked cardinal symptoms but of those border line cases. The presence of a murmur/

murmur over the gland is very common and occurs in 80 per cent of all cases and is a valuable diagnostic sign. Also the occurrence of diarrhoea without a definite cause and especially if the stools are foetid. The restlessness, a purposeful restlessness not a mere fidgeting, the history of muscular weakness, difficulty in going up stairs. Dr. Plummer of the Mayo Clinic gave me a sign which he said was diagnostic, it was almost impossible for a patient suffering from this disease to get up from the ground on to a chair that was more than 18 inches in height without assistance. Very significant also is a history of loss of weight with dyspnoea while the rapid and rhythmic character of the tremor is of great importance, care must be taken not to confuse this with the tremor of opium smoking, the morphia habit, that of alcoholism and excessive smoking.

There are cases of simple goitre where the goitre presses on the sympathetic and vagus nerves so called false exophthalmic goitre, cardiac and respiratory disturbances may be partly due to stenosis of the trachea due to pressure and partly from mechanical injury of the nerves of the larynx. The cardiac derangement consists anatomically and clinically/

clinically in hypertrophy and dilatation of the right heart, it is supposed to be brought about partly by mechanical injury to the venous circulation and partly by difficulty of respiration, compression of the nerves of the heart may be also a contributing factor. There are others who say that the thymus has been too much neglected, it is enlarged in 85 per cent of the cases and its enlargement causes the cardiac symptoms by actual pressure on the base of the heart and great vessels but also many of the nervous symptoms are caused by direct pressure on the vagus, sympathetic and the phrenic also that the mental symptoms are caused by the interference with the drainage of the brain. This to me seems well nigh impossible for though there is enlargement of the thyroid it is in very few cases that there are pressure symptoms and as regards the thymus how can it exert such pressure without causing more vital damage.

In exophthalmic goitre the blood pressure shows the same anomalies, but to a less degree than those seen in aortic regurgitation. The pulse pressure is high compared with the diastolic, both systolic and pulse pressure are higher in the leg than the arm. Nontoxic goitre on the other hand/

hand does not give rise to this difference, the pressure in both upper and lower limbs being equal. This differential arm and leg pressure although characteristic of exophthalmic goitre is by no means pathognomonic. Identical pressure in arm and leg are regarded, however, of considerable value in ruling out this type of goitre. Also paralysis agitans has to be ruled out, as sometimes the symptoms are not unlike those of exophthalmic goitre but the age and history are the determining factors.

The introduction and the study of the basal metabolic rate has greatly facilitated the diagnosis of this disease and I have no hesitation in saying that this is specially useful in those border line cases which are so difficult to diagnose.

#### TREATMENT

In discussing this disease with medical men I have been struck with the number and variety of the modes of treatment, and the confidence with which the most diverse treatments are guaranteed as specific, and this tends to prove that something is more effective in favourable treatment than mere drugs. The thorough study of the individual in each case is an essential requisite to successful treatment.

HYGIENIC/

HYGIENIC MEASURES are of great importance, the finding out and the removal of all sources of focal infection, such as pyorrhoea, alveolaris, septic tonsils, chronic appendicitis, or gall bladder inflammation, the connection of pelvic disorders, the restitution of the normal drainage of the gastro-intestinal tract, the correction of gastric disorders, anti-syphilitic remedies where the Wassermann reaction is positive, anti-rheumatic measures where rheumatism appears to be connected with its origin, these will improve the patient's condition if not actually cure the disease.

The muscular weakness, the condition of the heart, the nervous irritability and the increased metabolism all indicate the necessity for rest, absolute mental rest and quiet and as complete physical rest as possible, and I have found that this is best obtained away from the patient's own home. This rest should be insisted on so long as the patient is losing weight. Regarding mental rest, any cause of mental distress or apprehension should be found out and the unburdening of the patient's mind is often the first step towards her cure. I have a patient and the cause of her mental distress is a sexual basis, a too vigorous and amorous husband/

husband. This is where the psycho-analyst professes to find out the cause and say, he is able to cure this disease but surely every doctor is able to find out any cause of the mental distress without running through the whole gamut of these often distressing awkward and harmful questions that this so called specialist uses. It is quite certain that the personality of the patient's doctor and the keenness he evinces in his methods, have much to do with the curative effects of the latter; for whatever the thyroid pathology is in exophthalmic goitre, the nervous and psychic elements of the disease, whether they be primary or secondary, are of very great importance in connection with the treatment of individual patients.

Naturally in the more severe cases more rest is required, but in all cases especially when the earliest manifestations appear, absolute rest should not only be prescribed but care must be taken to see that orders are carried out, thus after prolonged rest, cases are cured, hence the importance of early diagnosis.

Fresh air is essential in the treatment and lying out on a verandah or in a shelter all night if practicable is good.

In/

In less severe forms of the disease a moderate amount of exercise in the open air is beneficial, but dancing, sight seeing, going to theatres, picture galleries, shopping, and too frequent tea parties are to be prohibited as they all fatigue the patient too much.

Change of air is good, a dry cool bracing inland climate where the patient lives in the open air by day and night is the ideal to be sought for. I have found that sea air is unfavourable as my patients always feel tired and high elevations are not favourable to the heart and nervous symptoms.

HYDROTHERAPY daily baths or showers at the patient's body temperature are good as the increased action of the skin needs hygienic treatment, but depressing and exhausting baths are to be prohibited. I have found that a warm bath at night promotes sleep and is very useful especially as so many of these patients suffer from insomnia.

MASSAGE is very useful to those confined to bed if not carried to the point of fatigue.

DIET should always be varied as much as possible a plain abundant nutritious diet is necessary; small, frequent meals are better than a few large ones.

Milk /

Milk, Buttermilk, 'soured' milk are all useful but all stimulants, spices and condiments, such as alcohol in all forms, coffee, tea, curries, also all indigestible and stimulating foods are to be prohibited. Meat which is rich in proteins is to be but rarely given, and the patient gets on better without any meat at all, if she can put up with this hardship. It has been found that thyroidectomised dogs suffer severely, when fed on meat, they recover when fed on milk, carnivora in general suffer seriously, herbivora least from this experimental operation. Obviously, the thyroid must contribute to the breaking down of meat proteins, indeed proteins have been found to increase the activity of the thyroid, and a diet free from protein and rich in carbohydrates, tended to the opposite. Our aim being to inhibit the activity, all butcher meats, soups, fowl, fish and oysters even, are prohibited, and feed the patient on milk only, and its varied products, butter, cheese, cream, buttermilk, milk puddings, also ripe fruits and vegetables in abundance. Acidosis must be watched for and the saliva frequently tested with litmus. Vichy with its sodium bicarbonate is useful in neutralising any Phosphoric acid the blood may contain, and thus, in addition to protecting the kidneys, eliminates/

eliminates another source of thyroid excitation.

Thus the diet in hyperthyroidism should contain the minimum amount of protein foods.

I always put these rules drawn up by OCHSNER of Chicago into the hands of my patients, for I find that the active co-operation of patients suffering from this disease is more of a help than a hindrance in the cure.

- I. You should avoid all excitement or irritation like attending receptions, shopping, church work, or politics.
- II. You should get an abundance of rest by going to bed early and taking a rest after lunch.
- III. You should have an abundance of fresh air at night, sleep with wide open windows or on a sleeping porch.
- IV. You should drink nothing that irritates the nervous system like tea, coffee, or alcohol, of course you should never use tobacco.
- V. You should eat very little meat, if you are very fond of meat, take a very little beef, mutton, chicken, or fresh fish once or twice a week - at most thrice.
- VI. You should drink a great deal of milk, a quart per diem at least, and eat things prepared with milk, as milk soups, milk toast, milk puddings, etc., cream and buttermilk are especially good for you.
- VII. You should avoid beef soup, beef tea, and every kind of meat broth.
- VIII. You should eat an abundance of cooked fruits and cooked vegetables or very ripe raw fruits and drink fruit juices.

IX/

- IX You may eat eggs, bread, butter, toast, and cereals of all kinds.
- X You should drink an abundance of good drinking water or if this is not available, you should boil your drinking water for twenty minutes, cool and allow it to aerate or drink distilled water.

BOWELS-important in this condition is the fact that the intestines owing to nervous disturbances may fail to carry on the functions, thus causing a retention of faecal matter which itself can through the production of toxins by the colon bacillus colonies provoke considerable thyroid reaction. A saline purgative sodium sulphate preferably followed up, if need be, with sodium phosphate, a teaspoonful in a glass of hot water each morning to prevent constipation, will usually suffice to eliminate this source of excitation it is of the utmost importance that the bowels be kept regular and if the arrangement of diet does not cause a daily evacuation then enemata, lavage and washing out the bowel must be carried out. There is a theory that it is from toxins elaborated in the intestinal tract that the thyroid is stimulated in a pathological manner and the secretion which is excessive - a defensive arrangement - causes all the symptoms of exophthalmic goitre hence the importance/

importance of careful attention to the bowels.

ELECTRICAL TREATMENT includes the application to the thyroid of static, galvanic, and faradic currents, all of which appear to be of doubtful efficacy. It is probable that the suggestion is the cause of any improvements and since suggestion is of great value this treatment should be used. Also there is no doubt that this electrical treatment has a tonic action and so is useful. Regarding the treatment of this disease by Rontgen ray, in the published proceedings of the Royal Society of Medicine, London, July 1921, there is a report of various London physicians and surgeons on the treatment of exophthalmic goitre and there was a great diversity of opinion expressed. Some were against this method of treatment as it causes fibrosis of the gland and there is no knowing how far this process may go, it may even go on to cause myxoedema a worse condition than exophthalmic goitre. Also there is the risk of burns, and the danger of turning an innocent goitre into the malignant form. Others said it was good treatment and recommended that it should be tried on every case, for they say it reduces the pulse rate almost at once, tremor and nervous symptoms improve from the start, the gland rapidly diminishes in/

in size and the gland becomes softer. The advantages are summed up as follows:-

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1. No fatalities.
  2. No resulting scar as is seen after operation.
  3. The treatment does not interfere with the patient's occupation.
  4. It is painless and causes the patient very little inconvenience.
  5. If unsuccessful, an operation can be done with less risk because of the favourable action of Rontgen rays on the gland and on the thymus.
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This treatment should not be undertaken except by experts in Rontgen Therapy, the dose must be accurately measured, if the rays are applied in a haphazard manner, without knowledge of the total dosage, the result may be unsatisfactory resulting in serious burns or total destruction of the gland causing myxoedema. The duration of the treatment should be from 2 to 3 months, Coolidge tube to be used, average dosage should amount to 4H = 5 Holz-knecht or 10 x Kienbock or 1 B Sabourand Norre. This is the dose necessary to produce slight erythema some say this dose is too severe. Target of the tube should be at a distance of 10 inches from the skin, the filter should consist of 4 mm. of aluminium/

aluminium and one thickness of leather imposed. The dose should not be repeated inside 3 or 4 weeks.

I have tried this Rontgen ray treatment on some of my patients and I have not found the benefit claimed, - in fact, I found the proceeding was feared, the dark room, the noise, and the suddenness of the sparking were terrifying. Also I found that the gland was not reduced in size, in fact the opposite occurred, the gland was made larger and in some cases painful. There is another disadvantage: this treatment is costly and many middle class patients cannot afford a large sum, and the charitable institutions do not care for such expensive treatment to be given free.

**MEDICAL TREATMENT.** Very much could be written on the number and uses of the drugs that are supposed to be specifics for the cure of this disease. The practice was to use drugs and many drugs, now the consensus of opinion is, that the fewer the drugs given, the better it is for the patient; McCARRISON says that drugs should be given as little as possible and only when there are definite indications for their use.

Tachycardia should quickly subside under rest/

rest, no drug should be given for the heart in the beginning of treatment unless rest is secured. If rest alone does not quickly reduce the pulse rate, an ice-bag should be put over the heart constantly or intermittently.

Of cardiac stimulants digitalis only should be given when there is cardiac weakness and even then carefully watched as arrhythmia and gastric irritation may be caused by it. If it is necessary to give this drug it should be omitted every third or fourth day according to the condition. Some say that digitalis does not produce any slowing of the heart's action in this disease, but this is not my experience for I always give this drug if there is any cardiac weakness and it does steady the pulse. To the digitalis I add

Ammon. brom. gr<sup>v</sup> and lig. arsenicalis in III and I find this mixture does good in all my cases .  
Tinct. Belladonna minims 10 to 15 T.I.D. is supposed to soothe the nervous system and diminish the excitability and restlessness, possibly it may lessen the activity of the thyroid, but Belladonna does not have this effect on all cases, also it cannot be given continuously over a long period.

The best treatment for nervousness, restlessness, and insomnia is rest, fresh air in a cool bedroom /a

bedroom and a comfortable bed, the temptation is to give sedatives and hypnotics. These can be given in certain cases but these drugs are depressing. Opiates should not be given for this very reason.

Jackson and Mead of Boston recommend the use of the neutral salt of hydro-bromide of quinine grs. V T.I.D. and McCarrison also recommends the use of this salt, it has to be given for at least two years. I have given this drug for months and I do not find that this drug does what is claimed for it namely lessening the pulse rate, diminishing the sweating and tremor also decreasing the size of the thyroid. I have a patient who has steadily taken this neutral salt for fifteen months and she says she feels the lack of it when I stop it, but I do not know how much the psychical element comes into this case.

Intestinal antiseptics such as Salol, Buaphthol, thymol, benzo-naphthol, I have tried, but how can any of these have any antiseptic effect on the organisms in the lower bowel without damage to the delicate tissue and cells of the villi. The best results have been obtained from changing the flora of the intestine by giving a purely milk diet, to me this seems to be the best method of research in such a disease as this.

Calomel/1/

Calomel, I have found good as an intestinal antiseptic and a dose given every fortnight makes a marked improvement especially when combined with the neutral salt of quinine hydro-bromide. Iodine and iodides have been used a great deal in the treatment of this malady and sometimes do reduce the size of the gland; some patients may improve under these drugs but others are made worse complaining of headache, palpitation, nervousness, etc., and though the enlargement of the thyroid does decrease it does not mean that there is reduction of the hyperthyroidism.

Medical treatment should be carried out on general principles and complications must be dealt with as they arise. Dyspepsia, diarrhoea, constipation treated with appropriate remedies, and I have found that the dyspepsia is troublesome, needing a constant variation and change of drugs and I have not found that the regulation of the diet removes this symptom.

Tinct. convalarria, chloride of calcium, sodium phosphate, cod liver oil, are all described as specifics but so many drugs are mentioned as specifics and I have found that cases recover with rest/

rest and without giving drugs.

Suggestion does play an important part in the cure, and so all successful methods of treatment of such a disease should be utilised in a rational manner, but hypnotic suggestion is unwarranted.

ORGANOTHERAPY. Very soon after the use of modern organotherapy, thyroids, fresh and dried were tried, in some cases where myxoedema supervened on exophthalmic goitre of long standing, it does good, but otherwise it is contra-indicated as it only increases the symptoms. The thymus is usually enlarged in cases of this disease, so naturally it was thought this enlargement was compensatory, thus doses of thymus gland have been tried, both in the fresh, and dried form, without any definite results. Also ovary testes and adrenals have been tried without any better results.

The milk of thyroidectomised goats had its vogue, but it is not used so much now as the results do not correspond with the great reports given when this treatment was first floated upon the medical world.

Antithyroid serum prepared from the blood of thyroidless sheep has been employed, but here again the results expected have not come up to expectations/

expectations.

VACCINE TREATMENT. The coliform organism from the bowel in several cases where intestinal toxoemia has been supposed to be the responsible etiological factor, in the form of a vaccine has been tried. There seems to be some good done by this method of treatment, and it should be tried. In the case of COCKEURN on whom I tried, not an autogenous but a polyvalent vaccine, there was a remarkable change made in the diminution of the proteolytic Gram negative Coliform organisms, and what is the significance of these changes? I should like to try this method of treatment on a large number of cases, and hope to do so, if the opportunity is given me.

In cases of exophthalmic goitre which are due to some infection, tonsillar, dental, gingival, nasal, aural, intestinal, vaginal, hepatic, the causal disorder whatever it is must be removed, and this is where surgical aid is most fruitful. Last year when I was at the Mayo Clinic, 27,000 patients had, during the past year, their teeth and jaws x-rayed and none of these patients had come primarily complaining/

complaining of their teeth, but this method was used to find out any focal infection at the roots of the teeth, If intestinal stasis is suspected, bismuth meal and fluoroscopic examination are indicated; if present, high enemata, with the patient lying on the right side to enable the injection to reach the coecum, are the measures indicated. Half measures are futile, because the gland persists secreting abnormally, as long as the slightest toxæmia exists. Once this point is reached, rest, diet and the remedies described above, bring on lasting cures, provided they are persisted in, until the tachycardia has totally ceased, and fails to return with graduated exercises.

**SURGICAL TREATMENT.** At the Mayo Clinique and in the United States of America generally, the surgical world would say that thyroidectomy is the only rational method of treatment in exophthalmic goitre, and, therefore, every case should be operated upon, and the earlier the better - this may be because the type of this disease is much more severe, and appears earlier over there, than here at home.

A large portion of the thyroid, usually the whole of the right lobe, all the isthmus and a varying proportion of the left lobe are removed -  
the/

the higher the basal metabolic rate the more of the left lobe is removed, I saw as much as  $\frac{2}{3}$  rd. of the left lobe removed in more than one case at Rochester Minn. But after all this operative procedure is empirical the cause is not attached, only a symptom, also it is absurd to call these cases cured for though the symptoms may be lessened in severity, a very few can honestly be labelled cured. What is wanted is the after history of each case for a period of twenty years after operation. If it could be proved that the essential and fundamental cause of the disease is hypertrophy, and over-activity of the thyroid gland the best method of treatment would obviously be to reduce the enlarged gland to something like normal proportions. Unfortunately the operation has its own dangers, these are greatest in that class of case which responds least to medical treatment. Also after operation hypertrophy of the remaining portion of the gland may occur, and I heard of more than one case in which three operations for removal of portions of the thyroid gland were done, the surgeons said sufficient had not been taken away at the original operation.

The/

The mortality has been greatly decreased, and in the hands of experienced surgeons who are constantly operating on the thyroid, the risk has been greatly lessened, but this risk is not to be passed over.

In reading the report of the Royal Society of Medicine for 1921, mentioned above, I was much struck by the words of Mr. JAMES BERRY who has the best and greatest surgical reputation for thyroid-ectomy in Great Britain and knowing him personally, for he operated on an exophthalmic case of my own, he says, "a wider experience has led me to take on the whole a somewhat less sanguine view of the advantages of operation than I did in 1914, mainly on the ground of the tendency to relapse after even the most successful operations, and the incompleteness of the cure in many cases that at first sight seemed most favourable". In the case that Mr. BERRY operated upon, that I am concerned with, the exophthalmos never a very prominent feature has disappeared, the tremor has gone, except when the patient is over fatigued, but the muscular weakness is still present though in a lesser degree and the heart is still enlarged. Occasionally there are still attacks of paroxysmal tachycardia though less frequent, and the patient is still excitable, irritable/

irritable, and nervous though all these symptoms are improved. I cannot at present, 18 months after the operation count her a 100 per cent cure.

The frequency of recurrence after operation together with incomplete relief afforded in a large percentage of cases, demand that the patient should have the benefit of something more than a simple ligation of the blood supply, or the partial extirpation of the gland, in order to produce final and permanent condition of good health. The surgeon as a rule does not have the experience, the time nor the attitude towards the problem of medical treatment that is characteristic of the physician. Evidence is not wanting that with increasing experience many surgeons appreciate in a way they did not in the beginning of their thyroid work the necessity for medical supervision, and direction of the patient following operation, but the writer is convinced that the interest of the patient in dealing with so intricate, and complex a problem will best be served by the co-operation of a physician, and surgeon who have a sufficient amount of respect for each others ability, and integrity, to enable them to work in harmony in deciding the course/

course to be followed in any given case.

It is by seeking the primary cause, and eradicating it that the physician will cure his cases. This, however, is subject to the proviso that he will not neglect the collateral factors, absolute rest, bland diet, and careful avoidance of drugs that excite the thyroid. If after removing the primary source of intoxication, the gland after a reasonable time, is still causing trouble through structural changes or hypersensitiveness, then the many excellent measures are at his disposal, arterial ligation, partial thyroidectomy, hot water or quinine, and urea injections, x-ray and radium to finish the good work, and do full justice to his patient.

CONCLUSION/

C O N C L U S I O N .

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As regards treatment of exophthalmic goitre the symptomatic treatment of this disease generally resorted to, compromises the chances of the patient's recovery leaving unassailed the principal cause of the disease.

Many patients are subjected to thyroidec-  
tomy entailing risks, and morbid after effects, who could be cured by medical treatment, and the latter aim to remove the primary cause of the disease, and its morbid effects.

The remote result of surgical treatment would be greatly improved, were removal of the primary cause of the disease, and its morbid effects first ensured.

Probably all cases of exophthalmic goitre are due primarily to some toxin originating from some pathological process in one or more organs either tonsils, gums, sinuses, nose nasopharynx, teeth, stomach, intestine, genito-urinary organs, nervous system etc.

It/

It is even said that the cases due to emotional stress have as their primary cause, toxic wastes formed in the cerebrospinal neurons subjected to stress cholin, phosphoric acid, and particularly neurin, a highly poisonous waste product.

These poisons by exciting the thyroid apparatus to supranormal activity, owing to the active part taken by this apparatus in the defensive functions, cause it to secrete excessively, thus producing an additional toxicosis. The thyroid autocoid particularly when produced in excess, taking part also in tissue katabolism breaks down fats including fatty bodies in nerve and brain cells, thus accounting for the striking nervous phenomena of this disease. Exophthalmic goitre thus becomes the product of a vicious circle in which three toxics may take part, the primary causative poison which excites the thyroid apparatus, excess of the thyroid autocoid as a second poison, excess of katabolic wastes due to the autocoid as the third poison.

Timely removal of the disorder which produces the primary causative poison by arresting the excessive thyroid activity will thus prevent this triple/

triple toxicosis, and cure the disease.

Treatment must aim at removal of the effects of the poisons to insure cure, dropping symptomatic treatment as an empirical method unworthy of modern science.

#### AS REGARDS ETIOLOGY.

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The pathology, and etiology of exophthalmic goitre are as yet not fully worked out, and the primary causal factor has not been demonstrated.

One school of thought believes it is the sympathetic which works on the thyroid gland causing an increased secretion, and poisoning by the thyroid autocoid. Another school says it is the thyroid gland which is at fault, and the secretion affects the sympathetic thus bringing about a vicious circle.

Others say it is a toxin formed within the body, probably the gastro-intestinal tract. It is interesting in this connection as MCCARRISON has pointed out, there is a condition of hypo-acidity of the gastric contents as a general rule, and this favours infection of the upper parts of the/

the alimentary tract by microorganisms of disease. The frequency with which such disorders of this tract precede the onset of exophthalmic goitre is becoming increasingly evident with the more careful study of the patient's history. So many of the morbid changes seen in this disease suggest toxic infection.

The lymphocytosis, lymphatic hyperplasia which is seen all over the body, lymphocytic infiltration of the thyroid, liver and other organs, the chronic toxic inflammatory changes the thyroid, liver, and pancreas, the changes in the muscle, changes in the nervous system, changes in the adrenals, all these seem to point to a condition of chronic toxic irritation as the underlying factor in their production, and the gastric intestinal tract as the most common source of the toxic irritant.

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