THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given Arnold Stevens Jackson final oral examination for the degree of

Master of Science in Surgery

We recommend that the degree of

Master of Science in Surgery

be conferred upon the candidate.

John J. Pemberton
Chairman

A. C. Broders(?)

E. T. Bell

W. J. Penson(?)

Louis B. Wilson

Date

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REPORT

of

COMMITTEE ON THESIS

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Arnold Stevens Jackson, for the degree of Master of Science in Surgery. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

J. E. Lemberton

Henry A. Plummer

E. D. Judd

A. W. Strachauer

THESIS

DISEASES OF THE THYROID GLAND

Arnold Stevens Jackson, B.A., M.D.

Submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

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A Brief Review of the Anatomy, Embryology, Histology, Physiology, and Biological Chemistry of the Thyroid Gland.

Anatomy.-- The thyroid is a ductless gland situated in the front of the neck upon the lateral surface of the thyroid and cricoid cartilages and upon the anteriolateral surface of the upper end of the trachea. It consists of two lateral lobes united by a narrow transverse portion, the isthmus. The lobes are somewhat cone shaped and measure about 2 in. in length, 1½ in. in width, and ¾ in. in thickness. These dimensions vary considerably depending upon the age, sex, place of residence, and the general health of the person. The thyroid is relatively larger in infants than in adults, forming about one eight-hundredth part of the body weight in the former and one eighteen-hundredth part in the latter. The average weight of the gland is about 30 gm. but it may vary from 20 to 60 gm. depending upon the factors mentioned. It is reddish brown in color.

It is customary to speak of the upper portion of each lobe as the upper pole and the lower portion as the lower lobe. The remaining portion of the gland between is spoken of as the body. The thyroid and cricoid cartilages, esophagus, trachea, inferior laryngeal nerve, inferior constrictor of the pharynx, and the posterior part of the cricothyroid muscle are situated to the inward side of each lobe. Posteriorly to each lobe lies the carotid sheath, containing the common carotid artery, the jugular vein, and the vagus nerve. The prevertebral fascia and muscles, parathyroids, and inferior thyroid artery are also behind the gland. The sternohyoid, sternothyroid, and the omohyoid muscles lie on the anteriolateral surface of the gland. The sternocleidomastoid muscles just cover the lateral border.

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The isthmus, a narrow strip of gland usually overlying the third and fourth tracheal rings, is absent in about 10 to 15 per cent of cases.

Accessory and aberrant thyroids are fragments of thyroid tissue that occur anywhere from the root of the tongue to the arch of the aorta. Histologically they show the same structure as the thyroid gland. The so-called lingual thyroid is not uncommon. It may contain colloid or embryonal tissue and give rise to any form of tumor.

The parathyroid glands, usually four in number, are situated on the posterior surface of the thyroid gland. The upper pair are usually embedded in the gland substance, while the lower pair are in intimate contact with the branches of the inferior thyroid artery and recurrent laryngeal nerve.

Blood supply.-- The thyroid is one of the most vascular organs in the body. It is estimated that in proportion to its size it receives more than five times as much blood as the kidneys. Three vessels, the superior, the inferior, and the ima arteries supply the gland. The superior thyroid artery is a branch of the external carotid. As it enters the upper pole of the gland, it divides into the anterior and posterior branches. The subclavian artery gives rise to the inferior thyroid artery. The ima artery arises from the arch of the aorta or from the innominate artery and terminates in the isthmus. This vessel is not always present. The superior and inferior thyroidal vessels form a rich anastomosis in the gland. Crotti says, "If the four arteries are injected, not only the whole thyroid gland, but also the adjoining organs, as the trachea and the esophagus, will become injected at the same time. This is an important fact, as it shows that after ligation of all the thyroid arteries the gland may still receive blood from its collateral circulation."

The veins are not constant. The superior thyroid vein usually terminates in the junction of the thyroid, lingual and facial veins. The middle

vein when present, and the inferior thyroid vein, empty into the internal jugular vein. The imae veins empty into the innominate vein of both sides. Thyroid veins are valveless.

Lymphatic supply.-- There is an extensive lymphatic system. The small lymphatics form a network around each vesicle. Lymph spaces lie outside the perivascular capillaries. The union of these spaces with the interlobular vessels forms large trunks which anastomose into plexuses. Two main trunks run from these plexuses and carry the lymph to the circulation by way of the superior and inferior deep cervical glands.

Nerve supply.-- The vagus and the sympathetic (median and inferior cervical ganglion) supply the thyroid gland. The inferior laryngeal nerve, although in close contact with the gland, does not supply it. The superior laryngeal nerve, a branch of the vagus, does supply the gland.

Embryology.-- The thyroid gland is developed as a median evagination of the entoderm lining the floor of the pharynx at a level between the first and second branchial pouches, according to investigations by Müller, His and Verdin.

In the mesobranchial field, just in front of the second groove, a median invagination of the walls of the pharynx appears, forming a depression which becomes deeper and deeper, and finally forms the thyroglossus duct. At its lower end this duct bifurcates, forming two terminal buds which are composed of epithelium. These epithelial buds branch and re-branch, forming small epithelial masses in which closed epithelial-lined cavities appear. These compose the vesicles or secreting elements. The thyroid gland proper is formed by the union of most of the cell masses. Occasionally one of these masses becomes separated and wanders down towards the heart, giving rise to an accessory thyroid. The latter in turn may give rise to an aberrant goiter.

Histology.-- The thyroid gland is invested by a thin capsule of connective tissue which projects into its substance and imperfectly divides it into masses of irregular form and size. The projections are composed of white fibers and elastic tissue and carry with them the blood and nerve supply of the gland. The lobes are divided into lobules by other projections, and scattered throughout these lobules are numerous closed vesicles or follicles, in turn separated by a narrow septum. These vesicles are the secreting units of the gland.

The vesicles of the adult animal are usually closed spherical sacs, but they vary much in size and shape. They are from 40 to 300 microns in size. Each vesicle is lined by a single layer of epithelium which rests directly on the vascular connective tissue envelope. The vesicle in the thyroid gland has no basement membrane. The vesicular epithelium varies in height from low cuboidal to low columnar according to the condition of secretory activity of the gland.

The vesicles contain as a normal product a viscid, homogeneous, semifluid, slightly yellowish, colloid material; red corpuscles are found in its substance in various stages of disintegration. The yellow color of the colloid is probably due to the hemoglobin which is set free from the red blood corpuscles. Colloid makes up more than one-half the weight of the gland.

When the gland is in the normal resting stage the vesicles become distended with colloid and the epithelium is consequently flattened out. When the functional activity of the gland is diminished below normal, as in myxedema, the supply of colloid is increased. During the active stage of the gland the colloid diminishes and the epithelium becomes columnar. When the gland is exceedingly active, as in exophthalmic goiter, there is but little colloid, while the epithelium is high columnar. The amount of colloid depends apparently upon two processes, one of absorption and the other of secretion.

The cells may contain fine granules, and a spherical nuclei with a fine chromatin network.

Between the vesicles is a fine parenchymatous stroma containing the parenchymalcells from which new vesicles may be formed in case of need. The division of these cells into "principal cells" and "colloid cells" is unnecessary and misleading, according to some writers, since the different appearances represent different stages of the cell's activity.

Physiology.-- The function of the thyroid gland was little understood prior to Kocher's time. Wharton believed it was only of cosmetic value to give a well rounded appearance to the neck. Winslow, Morgagni, and other observers believed that a direct communication existed between the gland and the larynx, and that an excretory canal emptied into the region of the vocal cords. The thyroid was supposed to furnish a secretion for lubricating the cords.

Another view was that the thyroid was concerned with the circulatory system and exercised its function by exerting a mechanical pressure on the carotids, when the gland was filled with blood, thereby regulating the supply of blood to the brain. We now know that indirectly the thyroid does control blood pressure, so that this view was not as far fetched as it might at first appear to be. We also believe that the gland is supplied by vasodilator fibers from the superior laryngeal nerve and vasoconstrictor fibers from the sympathetic system. Stimulation of the sympathetic nerve increases the blood supply to the brain by causing a vasoconstriction. Stimulation of the central end of the superior laryngeal nerve decreases the blood supply to the brain by causing a vasodilation of the thyroid.

Sir Astley Cooper, in 1840, was probably the first to observe that condition which we now term myxedema, that occurs following thyroidectomy. He failed to pursue his observations, nor did he give them the correct inter-

pretation, and it was not until 1883 that Kocher clearly brought this condition to the attention of the world.

The function of the thyroid gland is intimately associated with that of the pancreas, the adrenals, the sex organs, the liver, the pituitary gland, the thymus, the cardiovascular, nervous, osseous systems, and with metabolism. Its relation to the parathyroid glands is still a debatable question.

The thyroid stimulates and is stimulated by the adrenals. We know that the medulla of the adrenal secretes epinephrin, a substance that raises the blood pressure by causing a vasoconstriction of the vessels supplied by the nervous system. There is ample proof that in diseases of the thyroid blood pressure disturbances occur. The work of Plummer on blood pressure and thyrotoxicosis is classic. He pointed out that adenoma with hyperthyroidism is usually associated with hypertension. On the other hand he said, "The high pulse-pressure with the well known vasomotor phenomena in exophthalmic goiter leads to the almost unquestionable conclusion that there is no vascular hypertension in this condition. The high systolic pressure is essential to the maintenance of a normal diastolic blood pressure in these cases having a low peripheral resistance. In many cases even a normal diastolic pressure is not maintained. That the long continued intoxication associated with hyperplastic thyroid may lead to hypertension is probable."

Goetsch has maintained that there is abundant physiological evidence to prove that increased thyroid secretion causes a hypersensitiveness of the sympathetic nervous system to the action of adrenalin. He has said, "If thyroid secretion sensitized the sympathetic endings to the action of adrenalin it was reasonable to suppose that a sudden increase of adrenalin in the circulating blood would call forth active responses throughout the domain of distribution of the sympathetic nervous system". He considered a positive reaction

would cause a rise in systolic and a fall in diastolic blood pressure. A rise of at least ten and sometimes of as much as fifty or more millimeters of mercury occurred in the pulse pressure. Together with these changes one saw an exaggeration of the clinical picture of hyperthyroidism brought out, especially the nervous manifestations.

The work of Sandiford, Boothby, and other observers, however, has not corroborated the findings of Goetsch.

Whether the thyroid gland exercises any influence on the disturbance of carbohydrate metabolism in relation with the pancreas and the adrenals has not been definitely proved. Fitz found that hyperthyroidism and diabetes in the same person are associated in a small number of cases. He believes there is no established evidence that such coincidence is more than chance. Diabetes usually follows the thyroid disturbance, but may precede it, and tends to parallel in severity the severity of the thyroid intoxication. He found that partial thyroidectomy for nontoxic goiter had no influence on diabetes, but that certain cases having toxic thyroid disease and diabetes, improved to a considerable degree after the thyroid symptoms are checked. Fitz believes this occurs because of a change in the rate of metabolism and not because a portion of the thyroid gland has been made functionless.

The thyroid acts with the pituitary body to influence growth and development. Removal of the thyroid in young animals results in their remaining small. There is a failure of the bones to develop and the cartilages and epiphyses do not proliferate. The skin becomes rough and infiltrated with a mucinoid substance, hence the name myxedema. The young animals remain apathetic and dejected; their movements are slow and awkward. The hair becomes dry and brittle and falls out. Anemia occurs. The muscular system becomes weak, and there is a marked change in the nervous system. In the human we find this condition existing in children as cretins and in adults as

myxedema.

That the thyroid influences the growth and development of the sex glands is evident from the fact that in young thyroidectomized animals the genital organs remain infantile. The testicles do not descend, and, as a rule, do not secrete spermatozoids; the ovaries remain small and sclerocystic.

The thyroid is supposed to interact with the thymus, through the agency of the lymphocytes, to regulate the supply of the excess of phosphorus in organic combination which certain systems, particularly the osseous and nervous, require during development and growth (Sajoris).

McCarrison believes that the thyroid inhibits the action of the pancreas, which is hyperactive in subthyroidic states, and regulates the storage of glycogen in, and its discharge from, the liver. Thus by its interaction with the liver, the pancreas, and the adrenals, it regulates carbohydrate metabolism. Its influence over calcium metabolism is exerted through the medium of the gonads, thymus, pituitary and probably other endocrine organs.

The relation of the parathyroids to the thyroid has not been determined. While these glands form an integral part of the thyroid apparatus, yet they appear to functionate independently of the thyroid.

That a definite relationship exists between the thyroid and the blood is evidenced from the severe secondary anemias seen in myxedema. In young thyroidectomized dogs a marked anemia is found. The blood becomes intensely venous in this condition, the amount of carbon dioxide greatly increasing, while the amount of oxygen is reduced sometimes 50 per cent. Vassale thinks that the red corpuscles have lost their capacity for fixing oxygen because he found that soon after intravenous injection of thyroid extract the blood loses its venous properties and becomes normal again. Possibly this may explain why thyroidectomized animals are so sensitive to slight changes in

temperature. The same reason may account for the great dislike of cold weather and the apparent comfort on the hottest days of myxedematous patients.

We have abundant clinical evidence of the relationship of the thyroid gland to the nervous system. That the gland exercises a definite function over the central as well as sympathetic nervous systems is indicated by the work of many investigators. Wilson and Durante reported in 1916 that they had found definite histological changes in the cells of the cervical sympathetic ganglia in hyperplastic, or exophthalmic goiter which occurred in all of the twenty cases they examined. There have been reported various and multiple lesions of the cerebrospinal system in thyroidectomized animals. According to Crotti, Albertoni and Tizzoni found peripheric neuritis; Weiss and Rogonitsch found anemia, edema of the nervous elements, and a parenchymatous encephalitis; Herzen and Löwenthal reported a vacuolar degeneration and atrophy of the pyramidal cells. Pisenti and Luppo found bulbar hemorrhages.

The thyroid gland exercises a profound influence over the osseous system. Removal of the gland in young animals results in a failure of the bony skeleton to develop, and of the cartilages and epiphysis to proliferate. The bones remain short and fragile, and calcification is incomplete. As pointed out by Gauthier, the fact that certain fractures do not repair normally and that the callus formation is retarded for weeks and months may be recognized as the result of thyroid insufficiency. Thyroid extract has proved of benefit in the treatment of some of these cases. Holmgren's belief that individuals affected with exophthalmic goiter at the time of their growth appear to have longer bones than normal is confirmed by my own observations at the Mayo Clinic. I examined two children for exophthalmic goiter both of whom were over six feet in height.

Probably the most important function of the thyroid gland is

that concerned with its metabolic activities. Though exhaustive studies on metabolism by Du Bois, Rubner, Benedict, Lusk and other investigators, we know that the thyroid regulates the oxygen intake and the carbon dioxide output. It also has an important influence in regulating the body temperature. The accumulation and repartition of fat in the body is governed by the thyroid. In diseases of the thyroid there is a marked disturbance of the basal metabolism. In exophthalmic goiter the basal metabolism may be increased ten fold. In myxedema, on the other hand, the metabolism is subnormal.

According to McCarrison the thyroid gland maintains the constituents of the blood -- the red cells, the white cells, the hemoglobin and salts -- at a proper level. It controls the metabolism of those metallic ions necessary for cellular activity, and of albumins, carbohydrates, and salts. It controls excretion by its physiological diuretic action on the renal epithelium and by its action on the liver cells and excretory organs of the body; in short it maintains the efficiency of all cells and thus speeds up and keeps at a healthy level every bodily function.

Mann was able to prove that the thyroid gland was not a factor of significance in hibernating animals.

Kendall believes that there is abundant evidence to show the dependence upon the ductless glands for the metabolism of nitrogen. The formation of intermediary products between ammonia and urea and probably other nitrogen constituents of the urine is brought about by the secretions of the endocrine glands. The thyroid hormone is involved in the first split of ammonia from the amino acids. The adrenal cortex secretion then converts this substance into some other, and the secretions of the thymus, the parathyroids, and other ductless glands are involved in the further elaboration of the nitrogen constituents which finally appear in the urine.

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Plummer believes that the function of the thyroid is to furnish a hormone essential to cell metabolism. He has said, "In regard to energy, the energy production of a gas engine, for instance varied as the rate of excitation of potential energy in the cylinder; that was also true of energy transformation in animal cells. All available energy became transformed into motion or heat on excitation. The thyroid hormone (isolated as a pure crystalline compound) was a catalytic agent controlling a quantum of potential energy for transformation to heat or motion, on excitation of the cell. At rest, fourteen hours after eating, the dynamic equilibrium was approached. The rate of energy production, twelve hours after eating, in a horizontal position, was thirty-nine calories per square meter of the body surface. The normal individual varied little from this. When there was little or no variation from this, there was no functional thyroid disturbance. The rate of energy production varied with the amount of hormone in the cells; the hormone remaining constant, the energy rate varied with excitation. Change of amount of hormone in the tissues caused change in the basal metabolic rate. These conclusions are corroborated by the medical and surgical aspects of the disease."

This brief resume of the function of the thyroid gland shows the extremely important part of this small structure in the development and control of the body.

Chemistry -- The record of the chemical study of the thyroid was one of the most disappointing of all the different phases of investigation of the gland. However, the brilliant work of Kendall, who has successfully isolated the thyroid hormone, thyroxin, has greatly stimulated interest in the chemical study of the gland.

In 1812, Courtois discovered iodin in the thyroid gland, and although it had been used in thyroid therapy for many years previous, its true

value was not recognized until this discovery. Since then its use has been universal in treating diseases of the thyroid.

In 1895 Bauman discovered in the thyroid an element that he called iodothyrin, which he considered to be the active principle of the gland. Later research established the fact that this substance, prepared by acid hydrolysis, does not exist as such in the thyroid, and at the present time it is not regarded as possessing pharmacologic properties the same as desiccated thyroid.

Crotti tells how Notkine extracted from the thyroid an albuminous substance which he called thyreoproteid. Given in subcutaneous injections to thyroidectomized animals it produces convulsions, dyspnea and death, whereas given to normal animals it causes symptoms resembling those of cachexia strumipriva. This substance is not normally found in the thyroid, but is a toxic product of metabolism, and is neutralized in the gland itself.

Beebe isolated a substance from the thyroid gland, thyroprotein, which he considered to be the active principle of the gland. Its therapeutic action has not proved as reliable as thyroid extract. Beebe and his co-workers, as well as Rogers, have isolated from the thyroid a substance which reduces blood-pressure on intravenous injection, but which apparently does not possess the other therapeutic properties of thyroid extract.

Oswald isolated two substances from the thyroid gland, which he called thyreoglobulin and nucleoproteid. The first one may or may not contain iodin. If it contains iodin, it is called iodothyreoglobulin. Nucleoproteid contains large amounts of phosphorus but no iodin.

In 1910 Kendall[6] began his attempt to break down the thyroid proteins by other means than acid hydrolysis, and to isolate the thyroid hormone. It was not until 1914 that he was able to isolate a crystalline substance containing 60 per cent iodin from the thyroid, which he called thyroxin. It is an indol nucleus to which is attached a side chain of three carbons terminating in

a carboxyl group, and on the alpha carbon to the nitrogen there is a carbonyl group.

Kendall found that in cases of thyroid deficiency the administration of this pure crystalline substance alone will relieve the symptoms, and furnish the same relief as desiccated thyroid itself. It appears that the physiologic activity of the thyroid is due to the presence of this substance.

The name, thyroxin, was given to this substance, because it appeared desirable to emphasize the presence of the oxy-indol nucleus, and it seemed equally desirable not to emphasize the presence of iodin. The substance was, therefore, named thyro-oxy-indol, which was shortened to thyroxin for everyday reference to the substance. At first, Kendall[7] believed the activity of thyroxin was due to the oxygen condensing with the amino group of an amino-acid, and the carboxyl group of the amino-acid reacting with the imino group of thyroxin. He has shown, however, that the physiologic activity of the substance is produced by the CO-NH groups.

The typical symptoms following the administration of thyroxin are increase in pulse-rate, nervous irritability with tremor, and increased appetite with later nausea and diarrhea. In order to produce these symptoms several successive daily doses are required before the animal or human being will respond. Kendall[8] believes that the continued presence of this substance in the body over a considerable length of time is required to call forth a physiologic response.

The typical picture of exophthalmic goiter cannot be produced in the normal experimental animal by the administration of the thyroid hormone alone. It appears highly probable, according to Kendall[8] that the first vigorous response to the administration of the thyroid hormone closely resembles the condition present in exophthalmic goiter, but because of the ability of the animal

to develop a tolerance these symptoms are very short lived. Kendall believes that in exophthalmic goiter the primary disturbance is not in the thyroid, but that this disturbance results in a long continued stimulus of the thyroid, and conditions are such that a sufficient degree of tolerance to the thyroid hormone is not developed. The difference is that in exophthalmic goiter the organism has the ability to remain in a hypertrophied condition. The normal experimental animal cannot continue to respond to the thyroid hormone in a similar manner.

In regard to the relation of iodin to the activity of thyroxin, Kendall[6] believes the presence of iodin in the compound must exert some influence, and it is probable that the presence of iodin renders the active groups more reactive.

Kendall[6] thinks that the active groups present in thyroxin are a necessary mechanism for the production of energy within the body. Plummer[17] has maintained that the thyroid hormone must fulfill this requirement.

Recently Kendall[9] has said, "Under normal conditions an equilibrium exists between the thyroxin in the thyroid gland, the amount in the blood-stream, and the amount in the tissues. It is probable that the amount in the tissues fluctuates according to the energy demands of the body, but that there is always an equilibrium seems highly probable.... Whether or not the thyroxin constant of the tissues diminishes after a period of great exertion, the thyroxin being carried back to the thyroid gland by means of the bloodstream and there held as a reservoir until further demanded, is still unknown."

Colloid, the principal constituent of the thyroid, is composed mainly of protein. It is insoluble in boiling water, alcohol, or ether. It stains readily with eosin and other analin dyes. Its staining qualities depend upon the degree of secretory activity of the gland. It contains besides iodin, its most important constituent, sodium chloride, cholin, phosphorus, sulphur, arsenic, bromine and lipoids.

The iodin content varies markedly in different localities. There is about three times as much iodin present in the summer as in the winter months. It varies somewhat with sex. Certain diet, such as sea food, influences the iodin content of the gland, as does the stage of its activity. Iodin is found in many organs, as the lungs, liver, kidneys, central nervous system, the adrenals, the spleen, the lymph glands, muscles, hair, thymus, etc., in addition to the thyroid.

Kendall [10-11] is now carrying on a series of experiments to determine the exact amount of iodin in the blood and tissues with a view of finding out the thyroxin content of these structures. This would determine the metabolic activity of the tissues and their energy output, and would greatly simplify the physiological problems of the thyroid.

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Historical Review of Goiter.

In spite of the fact that goiter has been a common malady for thousands of years, it was not until the work of Kocher and Bilroth between 1870 and 1880 that the successful treatment of this condition became generally understood. Previous to this time about two hundred operations had been performed for the cure of goiter, but the majority of these were comparatively minor procedures such as the enucleation of small cysts and adenomas, transfixation ligations, division of isthmus, etc. A few surgeons had performed successful lobectomies, but the mortality rate was very high, and the operation was considered a most dangerous one by many great surgeons. The brilliant English surgeon Liston, for example, considered such an operation a hopeless procedure. Sepsis, hemorrhage and the lack of anesthesia and proper instruments were the chief obstacles that confronted the surgeons between the period of 1800 and the time of Billroth and Kocher. With the advent of Listerism, of artery clamps and of local and general anesthesia the problems confronting the surgeon operating for goiter became greatly simplified. It was then only a question of experience and the perfecting of technic before thyroid surgery should be developed to the wonderful standard which it has reached today. This high state of perfection has largely been brought about through the work of Mikulicz, C. H. Mayo, Crile, Halsted, Judd, De Quervaine, etc.

Probably the best historical review of goiter surgery is that written by W. S. Halsted. This excellent work gives one a clear conception of the fundamentals of goiter surgery. It clearly sets forth the problems that had to be met and overcome one by one, problems that even today cause the less experienced surgeon much anxiety.

According to Halsted, the fundamental, historical papers are a tract by Hedenus (Leipzig, 1822), an admirable treatise by Mandt (1832) of

Greifswald, and a voluminous chapter by Günther (1864), professor of surgery in Leipzig. According to Mandt, "The early story of goiter is voluminous, but very tangled. Traces of attempts to distinguish varieties are found with the ancients; later, however, and especially in the Middle Ages, scrofula and other diseases of the glands were confounded with it and synonymously treated. This error was continued until late in the eighteenth century.....I think it probable that Abul Casem Khalaf Ebu Abbas, usually named Albucasis, undertook about the year 330 a genuine extirpation of goiter. He lived in Bagdad, was a bold and, one may say, venturesome operator, and could the better hazard the operation because of the following experience: A 'homo ignarus' had attempted a similar operation, and the patient having nearly bled to death from an injured artery Albucasis knew very well how to control the hemorrhage by ligature and the hot iron."

Several attempts made by French and German surgeons to remove growths of the thyroid gland are recorded in the seventeenth and eighteenth centuries. Halsted states that Desault in 1791 did a masterful excision of the right lobe, evidently for an adenoma, and that he was probably the first to ligate the superior and inferior thyroid arteries in the course of excision of a goiter, as well as to dissect the firmly adherent gland from the trachea. The description of this operation shows the remarkable skill which Desault possessed, for it was almost a century later before a marked advancement was made in the methods which he used.

Dupuytren practiced the method of ligating twice and cutting between ligatures, although this method was probably not original with him. He performed a remarkable thyroidectomy in 1817 removing in a bloodless manner a gland weighing two pounds, eight ounces. The patient, however, died thirty-five hours later from shock. It is interesting as well as instructive to note that Dupuytren, in ligating arteries, placed the first ligature on the cerebral side so that patients would not twice suffer pain. Many surgeons fail to recog-

nize the value of this important point even today.

Halsted calls attention to a peculiar idea in vogue by many of the surgeons of this period, that of bleeding exsanguinated patients, sometimes repeatedly, to reduce the fever of sepsis.

Benard reported a remarkable operation performed by Tillaux for hyperthyroidism in 1880. Not only was the operation remarkable, but the clinical history and pathological description are admirable. The symptoms are described thus:

"Attacks of suffocation, due partly to compression of the trachea and partly to compression of the recurrents; rough voice, difficulty in swallowing.... The eyelids close only with an effort; the sclera are visible around the cornea. There is continually a sense of tension in the eyes... On palpation the cardiac pulsations are strong, but there is no exaggerated thrill with the patient in repose; after walking, the pulsations become more frequent and the precardial impulse much stronger. Pulse 80; much quicker if the patient takes a few steps. Auscultation of the vessels of the neck shows continuous bruit with paroxysm. Appetite is good; no diarrhea. The patient has become irritable, flies into temper over nothing, is almost always in a state of very pronounced nervous agitation. There are frequently choreiform movements in the limbs. Diagnosis: Exophthalmic goiter, as plain as possible."

Luigi Porta, the great Italian surgeon, performed eleven operations for goiter; the first, in 1835; the last, in 1850. Five were merely ligations, and the others minor procedures as the enucleation of small tumors. He was the first to ligate the inferior thyroid artery, and it is remarkable that his first attempt consumed only three-quarters of an hour, the operation also including ligation of the superior thyroid artery.

The most important and the greatest number of operations for

goiter in Italy were performed by Bottini, who, like Porta, occupied the chair of surgery in Pavia. Bottini operated upon eighteen goiters with the mortality of 16.6 per cent. Most of Bottini's operations were of considerable extent, six of them being more or less complete excisions of the thyroid gland.

Possibly the first attempts at thyroidectomy for England as well as for the world were observed and described by Benjamin Gooch in 1776. These operations were attended with fatal results, and Gooch became strongly prejudiced against operative interference for goiter.

Sir William Blizzard was the first to ligate a thyroid artery (1811) for the cure of goiter. Death occurred from hemorrhage due to sepsis.

Patrick Watson, a famous surgeon of Scotland, achieved a remarkable success in goiter surgery in the early seventies. He perfected a special method of operating and practiced it systematically and with success.

Halsted found accounts of forty-five operations for goiter in America up to 1883. There were five deaths with an operative mortality of only 11 per cent. Among the early American surgeons who operated for goiter were: Nathan R. Smith, E. S. Cooper, E. L. Marshall, W. W. Greene, F. F. Maury and C. E. Fenwick. As pioneers in this work in America these men showed remarkable skill and fortitude in operating and combating the serious problems of hemorrhage and sepsis. H. G. Jameson was the first American and the tenth in the world to tie a thyroid artery for the cure of goiter. The ligation was made in 1821, only ten years after the operation of Sir William Blizzard.

In considering the early operations performed for goiter by the German, Austrian and Swiss surgeons, the work of Hedenus must be considered the most remarkable. At the very beginning of the nineteenth century he extirpated six suffocating goiters without a death, a feat which was not repeated for three-quarters of a century.

Dr. Klein of Stuttgart was probably the first to successfully remove a substernal goiter. Victor von Bruns, another great German surgeon, played an important part in the development of thyroid surgery. He was among the first to use the cutting edge of the knife to dissect the goiter from the trachea.

Theodor Billroth, although remembered chiefly as the pioneer of visceral surgery, performed more operations for goiter in the early eighties than any other surgeon. While professor of surgery at Zürich (1860-67) and at Vienna (1867-94) Billroth did about eighty-four partial or complete extirpations of the thyroid gland. His work at Zürich was done before the days of Listerism, and his mortality was so high (36.1 per cent) that he gave up operating for goiter for several years. From 1877 to 1881 he operated upon forty-eight cases (carcinoma excluded) losing but four cases (mortality 8.3 per cent). Antiseptic surgery and artery clamps were a great boon to his work.

Billroth was a great teacher, and his pupils, Mikulicz and Wölfler, did much to bring his teachings before the world and to carry on his work. Wölfler's monographs of Billroth's clinics are the best record we have of his surgery. Unfortunately the permanent outcome of the great surgeon's work was not as satisfactory as the immediate results, because in many cases the condition we now term myxedema developed from the total extirpation of the gland. Paralysis of the vocal cords also resulted in a number of cases. Billroth was among the first to remove goiters for merely cosmetic and not life saving purposes.

Wücke and Lick who preceded Kocher performed several operations for goiter in a creditable manner.

Kocher, generally considered the father of thyroid surgery, succeeded Wücke as director of the surgical clinic at Bern in 1872. Although

only thirty-one years of age at this time he shortly established a remarkable record for the removal of goiters, and within two years had done thirteen extirpations upon the thyroid gland. Among Kocher's most important contributions to our knowledge of thyroid surgery is the fact that total extirpation of the gland is followed by a condition which he termed cachexia strumiprivia. He was a pioneer in recognizing the value of ligation as a preliminary procedure to thyroidectomy in the cases with marked hyperthyroidism. Not only did he develop and perfect a remarkable operating technic that served as a stimulus for surgeons all over the world, but he made known the value and the wonderful results of operation as compared with the medical treatment of Grave's disease. Kocher's method of removing goiters under local anesthesia is just now coming to be recognized as the ideal method of procedure in many cases. He pointed out the danger of the indiscriminate administration of iodine to patients with goiter. Through his efforts the study of the pathology of diseases of the thyroid gland was greatly stimulated.

In 1898 Kocher reported 600 operations for goiter with only one fatality. This one was due to chloroform. At the time of his death, July 27, 1917, about 5000 cases of goiter had been operated upon in his famous clinic.

Mikulicz devised the method which is now used by most surgeons for resecting the gland.

C. H. Mayo today occupies the position formerly held by Kocher as the leading goiter surgeon of the world. Over 20,000 goiters have been removed at the Mayo Clinic, and great progress has been made in the perfecting of technic and the development of team work, so essential to the successful treatment of thyroid diseases. Through the work of Plummer and Mayo, toxic adenoma, a condition formerly confused with exophthalmic goiter, was recognized as a distinct disease. Through their work with the basal metabolic unit they have

perfected the diagnosis and basis of treatment of hyperthyroidism to almost a mathematical certainty. The operative mortality has been reduced to 3 or even 0 per cent on different groups of 100 cases.

Crile has likewise highly perfected thyroid surgery both by his own wonderful operative skill and by the development of remarkable team work on the part of his assistants.

Halsted, Bartlett, Judd, Pemberton, Sistrunk, Ochsner and others are among the leading American surgeons in this work today.

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The Geographical Distribution of Goiter.

Goiter is found in every inhabited country on the earth. McCarrison estimates the number of sufferers from goiter in Himalayan India and Europe alone at about 5,000,000. He states that in the two most goitrous villages in the Gilgit district in the Himalayas, there was scarcely a single goiter-free individual.

In France, Baillarger estimated in 1873 that the total number of adult goitrous individuals over twenty years of age reached 370,043, and that of cretins about 120,000. According to the statements of Mayet in 1900 these conditions have not altered appreciably.

In Europe goiter prevails most commonly in the Middle Alps, Switzerland being the greatest sufferer. According to Bircher[2], from 22 to 50 per cent of the school children and from 15 to 30 per cent of the recruits are goitrous in the districts on the right bank of the river Aare. The statistics furnished by Kocher show from 80 to 90 per cent of the school children of Berne to be goitrous.

In Austria and Germany there are great goiter belts where the disease prevails in endemic form. In the European countries cretinism and deaf-mutism are closely associated with goiter. Among civilized countries, Switzerland possesses the highest number of deaf-mutes. The statistics of 1871 show a general average for the whole country of twenty-four per ten thousand inhabitants as against three per ten thousand inhabitants for most countries.[2]
H. Bircher[3] says, "It is my belief that endemic goiter, deaf-mutism, and idiocy are only different degrees and ultimate results of one and the same degenerative process."

Goiter is so common in parts of England and Scotland as to be

distinguished by the names "Derbyshire neck" and "Withsdale neck".

In Spain endemic goiter exists in the Pyrenees, Asturia, and Galicia. It is commonly found in the mountains of Asia, Japan and many of the Asiatic Islands.

McCarrison states that goiter is most prevalent in temperate and sub-tropical zones. It is found, however, in regions of great cold, as in parts of Siberia, in Finland, and in the Hudson Bay country. It occurs also in regions of great heat, as in tropical South America, Borneo, Sumatra and Java.

While as a rule goiter is common in mountainous country, it is rarely seen in Norway and Sweden. Nor is it often seen in Denmark, the Netherlands, the North German Lowlands, the Scottish Highlands, and in the eastern and southern parts of the United States.

In North America goiter is common in the United States and Canada. It occurs especially in the region of the Great Lakes and along the St. Lawrence river. The disease is very prevalent in Wisconsin, Minnesota, Iowa, Michigan, Ohio, Indiana and Illinois. In certain districts in Wisconsin settled by the Swiss it may be considered endemic.

An interesting fact concerning goiter in this country is the rare association with cretinism that is so commonly seen in Europe. Deaf-mutism does not seem to be more prevalent in the goiter belt.

Prevalence in animals.-- In regions where endemic goiter is found, domestic animals are commonly affected. Marine found that 90 per cent of the street dogs of Cleveland are goitrous. Sheep, mules, horses, cattle, fish, rats, white mice, pigs, dogs, pigeons and fowls are all affected by goiter. McCarrison says that although fish of carnivorous habits, such as the pike, are more subject to goiter than are others, such as the carp, their susceptibility to it appears to vary greatly. Certain species of the

salmonidae have almost complete natural resistance to the disease; amongst susceptible species certain batches reared in captivity show a high degree of immunity.

It is interesting to note that goiter occurs more frequently in female than in male animals and that its occurrence is less in animals that are well fed and cared for.

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The Etiology of Goiter.

Despite the fact that our methods of diagnosing and treating goiter have greatly improved since Kocher began his wonderful work in the early eighties, our ideas regarding the etiology of goiter are still vague and obscure. For centuries people have dreaded certain waters believing them to be the source of goiter, yet in spite of a vast amount of research work along this line, we can only say that water is probably merely a vehicle for the transmission of some organism, the same as it is for the typhoid bacillus. For a long time there was thought to be some correlation between certain geological formations and endemic goiter, but this theory has now been pretty well disproved. We find goiter in the lowlands and plains as well as in the mountainous country. It occurs in the very cold as well as in the tropical climates. The fact that certain rocks, lime, magnesium, or chalk occur in goiter regions is no longer considered a factor in the causation of goiter.

Heredity apparently plays some part in the etiology of goiter. It is quite common to see a mother and several daughters suffering from this condition. The theory has been advanced that the excessive demand on the thyroid gland for iodin during pregnancy and lactation is responsible for the enlargement of the thyroid gland so frequently seen at this time. If the mother is unable to furnish sufficient iodin to the child, the latter may also become predisposed to this condition.

It is interesting to note that in a certain city in Wisconsin settled by the Swiss, about 80 per cent of the people show enlargement of the thyroid, and goiter is very common. Most of these people are descendants of the original settlers, yet in spite of the marked change of environment and climate goiter is even more prevalent than it was among the early inhabitants. Heredity may be an important factor here.

Because of the fact that goiter is uncommon along the Atlantic seaboard and the Gulf of Mexico, the idea has been advanced that iodin from the seaweed afforded a certain protection. The iodin content of the air and of the sea food was supposedly greater than for similar conditions in the central states. Goiter, however, occurs quite commonly in certain parts of the Pacific Coast. There is little of scientific value to support this theory. It is interesting to note that the great goiter belt in this country is in the region of the Great Lakes and central west and that the condition is far less common in the south and east.

Contact was never considered of much importance as a causative factor, and yet it may prove to be one of the principal means of conveying the condition. Colonel McCarrison, who has done as much or more experimental work on goiter than any other man, believes that the site of the infection in the human body is in the intestinal tract. He successfully treated a number of cases of goiter with thymol.

The infection theory as advanced by McCarrison is the one receiving the most consideration from authorities on the subject. Plummer believes that introduction of bacteria into the digestive tract is an important factor, if not the primary cause of endemic goiter. Many surgeons are attempting to remove the foci of infection as the teeth and tonsils in the treatment of goiter. Tonsillitis has long been considered as a possible predisposing factor.

McCarrison[7] believes that water is "the means of conveying the bacterial organism responsible for goiter. In a part of India in which goiter is endemic and where sanitary precautions are unknown, he found in studying the natives of eight villages situated along a single stream that the percentage of goiter increased the further down the river the village was located, and that the number of goiters was relatively low in a town situated on the river at a point where a fresh tributary joined it; the percentage again increased the

further down the river he went.

In a properly controlled problem, McCarrison[6] performed an interesting experiment on a number of soldiers including himself. In this work he used water, probably capable of producing goiter, which was then passed through a Berkfeld filter. The filtrate was used as drinking water for the soldiers under observation; a certain number of them showed a decided enlargement of the thyroid gland, accompanied by certain subjective symptoms, as throbbing in the neck, feeling of fullness and discomfort. The enlargement of the gland appeared about the fifteenth day and reached a maximum size about the twenty-fifth day. The soldiers acting as controls, who were given water known to be free of any possible contamination, remained normal.

McCarrison[5] in summarizing his views regarding the etiology of goiter states, "There appears to be no such thing as race immunity to the disease. It is doubtful to what extent heredity plays a part in the etiology of endemic goiter. The same exciting causes which produce the disease in the parent produce it also in the fetus and the child; a congenital instability of the thyroid mechanism, due to the action of goitrigenous toxins on the fetal gland, is present in a considerable percentage of all children born of goitrous mothers. Such children are, consequently, more apt to become goitrous in later life than those whose mothers are goiter-free.... The influence of the child-bearing period of life on the development of goiter is very great. In localities where goiter is not supposed to be endemic, as, for example, in London, the thyroid gland enlarges as a consequence of pregnancy in a little less than 50 per cent of all cases.....Goiter may develop in as short a space of time as ten days after exposure to goitrigenous influences; amongst young, susceptible newcomers to a goitrous district, a considerable proportion of cases develop within six weeks to three months after their arrival.....after a period of residence of eight years in such a center the majority of young people under the

age of eighteen become goitrous. Goiter shows a marked tendency to disappear when the sufferer leaves the goitrous district; it almost invariably reappears in such persons when they return to the infected locality.... Among predisposing factors are those which induce hyperplasia of the thyroid gland as rheumatism, rheumatoid arthritis, malaria, measles, and intestinal disorders... amongst factors which impose an added strain upon the functional powers of the thyroid are residence at altitudes considerably above that of sea level, defective air space, improper food or defective food supply, puberty, sexual activity, menstruation, pregnancy and emotional states, such as fright and continued mental strain... the lack of iodin in the air at altitudes above 1,000 feet will indirectly influence the thyroid towards hyperplasia by its lack in the food. The ingestion of waters charged with an excess of lime adds to the burden of the thyroid's numerous duties."

Lane, believing intestinal toxemia to be an important factor in the causation of goiter has advocated operations such as a colectomy that will short circuit the bowel and free the patient from intestinal toxemia.

The experiments of Marine and Gaylord in which it was shown that fish confined in tanks situated one above the other on a single water-supply show an increasing proportion of goiters from the highest to the lowest tanks seems to confirm McCarrison's observations with regard to the increase of goiter in villages situated one above the other on an open water supply.

In 1912 Gaylord found that by scraping the inner surface of the water-soaked wooden tanks in which the fish are confined, and in which the disease is endemic, an agent may be secured which produces thyroid hyperplasia and goiter when administered to dogs and rats, and which from its action on the mammalian thyroid when administered through drinking water, is no doubt the cause of the disease in the fish confined in the troughs. The agent is destroyed by boiling.

Goiter can be produced in animals--rats, goats--by feeding them on fecal material from goitrous and even non-goitrous subjects. This observation was confirmed by Sazuki in 1913, who also produced the disease in rats by the subcutaneous injection of rats' feces. McCarrison[3] found that 100 per cent of rats receiving the residue left on the candle of a Berkfeld filter after filtration of an emulsion of feces from a non-goitrous resident of a goitrous district showed large sized goiters, while the controls were normal.

McCarrison[3] was able to produce goiter experimentally in animals--rats and goats--by feeding them on cultures from the feces of goitrous subjects. He says that congenital goiter, cretinism, and congenital parathyroid disease, have been produced experimentally in the offspring of such animals by continuing to feed the mothers throughout pregnancy with these cultures. He has been able to cause the disappearance of recent cases of goiter by injecting vaccines prepared from intestinal organisms. In his opinion the facts demonstrate that the causal agents of goiter, as well as of its congenital manifestations, are microorganisms inhabiting the alimentary tract of sufferers from this disease. Epidemiological and experimental facts point to anaerobic organisms as the causal agents. The changes characteristic of parenchymatous goiter are due to toxic action and not to the presence in the gland of living microorganisms. The goitrous thyroid of endemic localities is invariably sterile.

These organisms reach the alimentary tract of man and animals by means of infected soil, food, or water, and there they flourish and produce toxins which, on absorption into the blood-stream, initiate the goitrous changes in the thyroid gland. Soil, water, and food are, therefore, vehicles only whereby the infecting agent or agents reach the body of men and animals. It seems almost certain that the great source of the disease is the infected individual, and that he is the producer, the reservoir, and the distributor or

"carrier" of the infecting agents. These agents are discharged from the body in the feces, and, it may be, in other ways not known to us, as, for example, in the urine and saliva.

A great amount of experimental work to determine the relation between the water supply and goiter was done by H. and E. Bircher and Kocher in Switzerland. Grange attributed goiter to the presence of magnesium in the water. St. Lager, to the presence of iron and copper pyrites. H. Bircher[4] came to the conclusion that goiter only occurs upon marine deposits and especially upon marine sediments and that all fresh-water deposits are free from goiter.

Dr. Repin, of the Pasteur Institute, has published several interesting articles upon the Nature and Origin of Goitrigenous Waters, which he associates with mineral springs. As a general proposition he affirms that endemic goiter is never absent in a mountain range of any importance, and that in proportion to the height and precipitousness the endemic is more intense. The disease attains its maximum upon the mountain slopes and adjacent valleys and plains, the upper zone being comparatively free.

The majority of evidence appears to be in favor of the infection theory and the work of McCarrison, Marine, and Gaylord and others seems to favor this view. In his more recent work, however, McCarrison[6] has made some interesting observations with feeding experiments on animals. He believes that lack of vitamins leads to diminished thyroid secretion. As a result of these experiments with pigeons and tadpoles which were fed various grain diet and iodin, with the production of goiter in varying degrees, he believes that there is such a thing as a "fat-thyroid, iodin balance". This balance may be disturbed either by an intake of iodin insufficient for the needs of the body or by the presence in the digestive tract of an excess of fat, more especially of an excess of free unsaturated oleic acid. Many possibilities suggest themselves as to

the action of bacteria in the gastrointestinal tract. Whether their activity is exerted on the iodin content of the body or on the metabolism of fats are questions for further investigation.

Brown believes that two sources of toxemia seem particularly apt to produce thyroid enlargement--namely, intestinal and oral. He says that we can understand why intestinal toxemia has this effect, since Kendall has shown that the active principle of thyroid secretion is an iodin compound of indol, a putrefactive decomposition product of the tryptophan in the protein molecule. It would appear as if the body provided in this way its own antidote, an increased production of indol necessitating and providing for more thyroid secretion. Quite as striking is the influence of oral, particularly tonsillar, sepsis.

Besides nutritional disturbances and toxemia, Brown believes that in Grave's disease the psychic factor plays a very large part. He says happy people do not get Grave's disease. There is often a history of shock, strain or psychic conflict. The factor of shock was shown repeatedly during the air raid on London and after the San Francisco earthquake.

Cannon was able to produce hyperthyroidism in cats by stimulation of the cervical sympathetic nerve. Many other experiments have been performed and theories advanced to determine the etiology of goiter, but this disease still offers one of the most baffling problems in the field of medical research.

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The Prevention of Goiter

While goiter is the cause of great economic and social loss to Europe and certain Asiatic countries, it has not been as serious a problem to the United States. The common association of endemic goiter with cretinism and deafmutism in certain European countries has increased this loss. Although in certain parts of this country the disease is almost as prevalent as in the Alpine districts, cretinism is rare and one seldom seen goiters of any great size.

From a sociological point of view the importance of this problem was recognized by several governments years ago. The Sardinian government as long ago as 1848 appointed a commission to investigate the causes of endemic goiter and to find a remedy for the disease. Since then similar commissions have been appointed by most of the European governments and by medical organizations in this country. In the United States, Marine, Gaylord, Crile, Mayo, Plummer, Kendall, in particular, have accomplished a great deal towards determining the etiology,prevention and cure of goiter. The work of McCarrison in India is remarkable. H. and E. Bircher, Kocher and numerous other investigators have carried on the work in Europe.

Goiters have been made to disappear for many inhabitants of Switzerland by a change of residence and the use of boiled water. Goitrous districts have been almost freed from the disease by change of water supply. Obviously one of the most important problems confronting certain districts in Europe is that of obtaining a water supply free from pollution.

Probably the commonest type of goiter seen in the United States is the simple colloid goiter of adolescence. At many of our large schools for girls this type of goiter is seen in from 25 to 60 per cent of the students.

In a survey of goiter among the school children of Akron, Cleveland and Warren, Ohio, Marine and Kimball[3] found the percentage relations of school children with normal and enlarged thyroids to be as follows: (1) Girls: 9679 (examinations extending through 3 years) were examined in Akron--51.36 per cent, had normal thyroids and 48.64 per cent had enlarged thyroids; 406 were examined in Cleveland-- 81.68 per cent had normal thyroids and 18.32 per cent had enlarged thyroids; 911 were examined in Warren-- 90.45 per cent had normal thyroids and 9.55 per cent had enlarged thyroids. They conclude,

"The general statements that sex makes no difference in the incidence of thyroid enlargements before puberty and that during and after puberty it becomes five or six times more frequent in girls do not conflict with our figures. The explanation for the apparent variance is that the majority of pupils examined were below the age of puberty."

Regarding the prevention of simple goiter in man, Marine and Kimball[2] have said:

"Simple goiter in animals is probably the easiest of all human diseases to prevent. Simple goiter includes all the thyroid enlargements seen in the lower animals and those thyroid enlargements seen in man, except cases properly classified as exophthalmic goiter. Many cases with simple goiter later develop exophthalmic goiter. In brief, simple goiter includes all those thyroid enlargements formerly classified as endemic, epidemic and sporadic. The periods when it most frequently develops are (1) fetal, (2) adolescent, and (3) during pregnancy."

In their opinion the amount of thyroid gland it is necessary to remove in order to cause compensatory hyperplasia varies somewhat with the species of animal, definitely with the age, the diet, and the presence of iodin. Even after three-fourths of the normal gland in cats, dogs, rabbits, rats, fowls

and pigeons has been removed, the remaining portion of the gland may be protected against compensatory hyperplasia by the administration of exceedingly small amounts of iodin.

Experiments have been done to prove that if most of the thyroid gland is removed before or in the early stages of pregnancy and rigid steps are taken to exclude available iodin, the pups at birth will have enlarged thyroids, as first shown by Halsted; while if available iodin is present, the pups will have normal thyroids.

Marine and Kimball repeatedly found that a milligram of iodin given at weekly intervals is sufficient to prevent thyroid enlargement, although without iodin other pups of the same litter, living in the same kennel, and eating the same food, regularly developed goiter.

At one time it seemed as if the sheep raising industry of Michigan would have to be abandoned because of the great prevalence of endemic goiter. It was largely by accident that the disease was overcome when the salt deposits around the Great Lakes were discovered. It was observed that sheep fed on this salt remained free from goiter. An analysis of the salt shows both bromin and iodin to be present.

In a like manner goiter threatened to destroy the artificially raised members of the salmon family and many plants were abandoned on account of the disease. Marine and Lenhart[6] solved the problem, and were able to completely overcome the disease by the use of very small amounts of tincture of iodine added to the water.

Smith reported similar work in the prevention of goiter in hogs. By the use of potassium iodid administered to the mother during pregnancy, he was able to completely prevent fetal myxedema.

For the prophylactic treatment of goiter among the Ohio school children, Marine and Kimball[2] used 2 gm. sodium iodid, given in 0.2 gm. doses

each school day, for each pupil in the fifth, sixth, seventh, and eighth grades; and 4 gm. given in 0.4 gm. doses each school day for each pupil in the ninth, tenth, eleventh, and twelfth grades. These amounts were given twice annually about the first of May and December, at the schools by the teachers or nurses.

In a recent publication Marine and Kimball[4] give the results of their prophylactic treatment for simple goiter which they have carried on in connection with the public health service of Akron. Their observations have extended over a period of thirty months. They found that of 2,190 pupils taking 2 gm. of sodium iodid twice yearly, five have shown enlargement of the thyroid, while of 2,305 pupils not taking the prophylactic, 495 have shown enlargement of the thyroid.

Of 1,182 pupils whom they found with thyroid enlargement at the first examination and who took the prophylactic, 773 thyroids have decreased in size, while of 1,048 pupils with thyroid enlargement at the first examination and who did not take the prophylactic, 145 thyroids have decreased in size. These figures demonstrate in a striking manner both the preventive and the therapeutic effects.

Marine and Kimball believe that "prevention of goiter in mother and fetus is as simple as that occurring during adolescence. Practically, it would seem that it is a charge or responsibility of individual members of the medical profession supplemented with public education.

"The prevention of goiter of adolescence, on the other hand, should be a public health measure under state, county or municipal control. The existing system of organization of the schools, public and private, is sufficient to handle all the details without additional aid or expense...Thyroid enlargement is approximately six times as frequent in girls as in boys.... In

this climate probably the maximum of prevention, coupled with the minimum of effort, would be obtained by giving it between the ages of 11 and 17 years. As applied to our schools it would mean beginning with the fifth grade.".

Regarding the effect of iodin on the thyroid gland, they believe, "This is effected in two ways (1) on the iodin store and (2) on the histological condition.... If the thyroid gland is not saturated with iodin (i.e., contains less than 4 mg. per gm. of dried gland) it is taken up readily by the cells following its administration in any form and in any manner thus far studied. An increase in the iodin content of thyroid may be demonstrated in a few seconds following the injection of a soluble salt into the circulation. Iodin thus taken up is held by the cells until elaborated into physiologically active hormone, when any excess is excreted into the follicular spaces and stored in the so-called colloid. Two factors are then concerned in the storage of iodin in the thyroid: (a) the capacity of the gland cells to take up and elaborate the hormone and (b) the capacity of the colloid material to store the product. It is evident, then, that to obtain maximum thyroid effects from a minimum amount of iodin, it should be administered in amounts not to exceed the capacity of the cells at any given time to handle it. The elaboration of the hormone proceeds slowly in the most active thyroids. Also when one recalls that from 4 to 5 mg. of iodin per gram of dried gland, or from 25 to 30 mg., is the total storage capacity of a normal thyroid, it is clear that small amounts of iodin (a few milligrams) given daily for a long period of time (a month or more) would produce optimum thyroid effects.

"Effect on histology of the thyroid. -- It has been shown that the minimum amount of iodin store necessary to maintain normal or quiescent thyroid structure is quite constant for mammals. In the dog, sheep, human and pig thyroid it is approximately one milligram per gram of dried gland, and

immediately the percentage is reduced below the minimum, hypertrophic and hyperplastic changes begin and continue until the store of iodin has again been raised above the minimum requirements, when involution takes place. This cycle may be repeated many times in the same individual under natural or experimentally controlled conditions. In young dogs, with active hyperplasia, involution is usually complete in from fourteen to twenty-one days after beginning the administration of iodin."

These experiments as well as those of Plummer at the Mayo Clinic and McCarrison in India are conclusive evidence that simple colloid adolescent goiters at least may be prevented and cured.

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Diagnosis, Symptomatology and Classification of Goiter.

In discussing the diagnosis and symptomatology of goiter the following classification will be found the most useful:

Exophthalmic goiter (Basedow's or Grave's disease).

Adenoma--
with hyperthyroidism (toxic adenoma).
without hyperthyroidism (simple adenoma).

Colloid goiter.

Malignancy, tuberculosis, or cysts of the thyroid; thyroiditis.

While it was pointed out by Möbius, as early as 1887, that in exophthalmic goiter there is an abnormally increased activity of the thyroid gland, and the classical signs and symptoms become well established early, yet even today this condition is confused with the form of hyperthyroidism seen in certain cases of adenoma. In 1911 Plummer[8] pointed out the difference between these two conditions. He stated that there are two separate and distinct clinical types of hyperthyroidism, each associated with a distinctive pathological change in the thyroid gland. In exophthalmic goiter the hyperthyroidism is always accompanied by hypertrophy and hyperplasia of the thyroid gland; in adenoma with hyperthyroidism this characteristic hypertrophy and hyperplasia does not occur, and the resulting clinical syndrome is distinguished from that occurring in true exophthalmic goiter.

The clinical differential diagnosis of the types classified above will first be considered. The pathological side will be reviewed in a following chapter.

Exophthalmic goiter.— Briefly, the following signs and symptoms are indicative of exophthalmic goiter. A history of rather rapid onset averaging nine months' duration is seen in this disease. Young men

and women (in a ratio of one to eight) between the ages of eighteen to thirty-five years are most frequently affected. Plummer has shown that the disease progresses by a series of waves extending over weeks or months. At the crests of these waves all symptoms are increased and a crisis results. During a crisis the patient is extremely nervous, emotional and irritable. Painless vomiting may occur for weeks; there may be diarrhea, or both conditions may be present. It is characteristic for the patient to pick at the bed clothes. He is unable to keep his extremities still. The slightest noise causes him to start and stare like a startled wild animal. He may not sleep or eat for days at a time. It is only during these crises that fever occurs, and the temperature frequently registers 104° and over. The pulse is rapid and seldom drops below 110. There is excessive sweating. Acute cardiac decompensation is frequently present. Edema of the extremities is a sequela. The pulse pressure is large; the systolic blood pressure usually registers 120 to 140 and the diastolic seldom rises over 75. There is marked weight and strength loss.

During the intervals between crises the patient may experience a false sense of well being. His appetite may be enormous at times, and yet in spite of eating five or six meals a day he may gain but little in weight. This is due to increased metabolism. His capacity for work, especially that requiring mental and not physical effort, may be greatly increased at first because of his keyed-up condition. Soon, however, the general muscular weakness, which especially affects the quadriceps group of muscles, renders him unable to do his usual amount of work. It is difficult for him to go up and down stairs, and he tires easily from walking. Perhaps his friends have noticed that he is more nervous than usual, or that his eyes have become unduly prominent. His heart pounds excessively and beats rapidly. In summer he suffers greatly from the heat; in winter a light covering is sufficient. Perhaps he has discovered a fine tremor of his hands, or that there is excessive sweating. An

enlargement of the thyroid gland is seldom noticed by the patient, and it is difficult to convince him that he has an "inward goiter". Occasionally the enlargement is such that even the patient detects a goiter. Once his attention has been called to the goiter, he may complain of tight or choking sensations or of sensitiveness on examination of the neck. The quadriceps -loss test, obtained by having the patient mount the examining table, is one of the most valuable indications of his ability to undergo operation. If unable to step up without assistance, the patient is in no shape for immediate thyroidectomy. Thrills and bruits over the superior thyroid vessels are present in nearly 80 per cent of all cases of exophthalmic goiter. Exophthalmos occurs within three months from the appearance of hyperthyroidism in an average of 50 per cent of the cases of exophthalmic goiter and within two years in 87 per cent.

In 1913 Plummer[9] pointed out the important points for differential diagnosis between exophthalmic goiter and adenoma with hyperthyroidism. In the latter condition enlargement of the thyroid gland is noted from five to ten years earlier in life. In exophthalmic goiter the symptoms of hyperthyroidism develop within a year after the onset of the goiter, while a period of fourteen and one-half years elapses before hyperthyroid symptoms become manifest in the adenomas with hyperthyroidism. In Plummer's studies exophthalmos occurred in 87 per cent of the cases of true exophthalmic goiter in which symptoms had lasted over two years. It was only rarely noted in cases of adenoma with hyperthyroidism. In 1915 Plummer[10] demonstrated in adenoma with hyperthyroidism a definite tendency to hypertension which is not found in exophthalmic goiter. In 1916[11] he established the probability of a different etiology in the two diseases.

Adenoma of the thyroid with hyperthyroidism.-- The onset of toxic symptoms in the adenoma group is both more gradual and less severe. It

is of a slow insidious type but with a more serious and lasting effect on the heart and kidneys. The acute crises do not occur. Thrills and bruits are very rare. The adenoma is present on an average of sixteen years before toxic symptoms become marked enough to bring the patient to a doctor. There is not the sudden loss of weight or the marked variation in appetite that occurs in exophthalmic goiter, although both conditions may be present to a lesser degree. In the older and more severe cases there is evidence of cardiac insufficiency with some edema of the legs and ankles. Myocardial degeneration evidenced by irregularities in heart rhythm is common. Boothby reported a series of 281 patients whose average age at the time of examination was 47.6 years. The average age of patients with exophthalmic goiter is approximately ten years younger. Whereas there is a tendency to hypertension in adenomas with hyperthyroidism, exophthalmic goiter is characterized by a large pulse pressure with a low diastolic and a rather high systolic reading, not as high, however, as in the adenomas. The average basal metabolic rate in adenoma with hyperthyroidism as shown by Boothby is plus 35 per cent. The rate averages considerably higher in exophthalmic goiter. Boothby reported three groups of cases for the latter condition in which the rates were respectively plus 66 per cent, plus 52 per cent and plus 36 per cent.

Adenoma of the thyroid without hyperthyroidism.-- Simple adenomas usually appear during or shortly after the age of puberty. They may enlarge so slowly as to be apparent to the patient only after many years, or may grow rapidly and early undergo degenerative changes through hemorrhage within the capsule of the adenoma, thus producing the various clinical types of cystic, hemorrhagic or calcareous goiter. The thyroid is asymmetrically enlarged, and one or more nodular tumors may be palpated. To palpate a small adenoma successfully it is necessary to grasp the gland firmly between the index finger and thumb while the patient swallows. These tumors usually cause

no symptoms for many years unless they press on the trachea. Frequently, however, the patient, if at all neurotic, will attribute a great many complaints to the goiter. Disfigurement of the neck often causes patients to have the adenomas removed. It is in this type of goiter that malignant degeneration most frequently occurs. Wilson states that the incidence of malignancy of the thyroid gland is one in 297 goiters at the Mayo Clinic, and that none of these patients gave a previous history of true exophthalmic goiter.

Symptoms of hyperthyroidism develop in 23 per cent of the cases, according to Plummer. Adenomatous goiters rarely cause toxic symptoms in persons under thirty.

Substernal and intrathoracic goiter.-- Intrathoracic goiter is defined by Judd as one in which the greater part of the enlargement of the thyroid is situated within the thorax. This type is to be distinguished from substernal goiter in which there is a projection of only part of the thyroid into the chest. The most common type is the fetal adenoma. Pemberton reports that an analysis of 4,006 thyroidectomies performed in the Mayo Clinic within a period of three and one-half years, for simple colloid and adenomatous goiters, showed 542 (13.5 per cent) were found at operation to be substernal, and twenty-five (0.6 per cent) of these were classified intrathoracic. The hypertrophied gland of the exophthalmic type is never seen in the totally intrathoracic goiter.

Lahey[4] has suggested that the pressure exerted by the depressor muscles of the hyoid and the sternomastoid may be a factor in causing these tumors to descend into the thorax. The influence of swallowing, ptosis of the larynx, gravity, flexion and extension of the head, and the development of an adenoma in an abnormally low thyroid, are considered by Pemberton as possible contributing factors. He believes that the anatomy of the region is such that extension of the growths developed in the lower poles should be downward behind

the sternum, along the path of least resistance. He also remarks that the influence of deep respiratory movements of the thorax in coughing, straining and the like, play an equally important rôle.

The history given by these patients is usually that of goiter of many years' duration, and in rare cases that of a goiter that gradually disappeared as it was drawn down into the thorax.

Colloid goiter.-- Plummer[12] has said that without definite knowledge of the exact mechanism we can assume that the normal stimulation of the thyroid is brought into play by partial exhaustion of the thyroxin in the tissues. Factors interfering with the production of this agent lower the amount delivered from the gland. There may be several such factors. The one known is an actual or relative shortage of iodin. A thyroid so handicapped, if sufficiently stimulated, can produce a normal amount or even an excessive amount of thyroxin; however, relative to the normally functioning gland, it tends to lag behind the demands of the tissues, that is, it does not respond quantitatively to stimulation as does the normal thyroid.... The human gland acting under these conditions deposits an excess of colloid in its acini. This constitutes the diffuse colloid goiter of adolescence. Diffuse colloid considered as an entity probably never hyperfunctions.

The terms simple, physiologic, or adolescent have been used to express this condition which is definitely a goiter of youth and will be considered here as one composed of colloid alone. With advancing age there frequently develop adenomas in association with the colloid goiter. Colloid goiters most frequently occur in young girls at puberty and are often spoken of as physiologic enlargements. They are soft and globular and cause a symmetrical enlargement of the neck. In a small percentage of the so-called vascular type, thrills and bruits are found, and when nervous symptoms, tachycardia and palpitation are present, it is difficult to distinguish these cases

from the early cases of exophthalmic goiter. It is rare, however, to find a history of rapid weight and strength loss, of exophthalmos, or of crises in these patients, while Plummer [12] has shown that in the majority of cases the basal metabolism is from 8 to 15 per cent below the average normal. The goiter in itself produces no symptoms but may be the causative factor in the production of many nervous manifestations. Some patients give no history of goiter, but come because of suffocation and choking spells, of difficulty in swallowing, and frequently because of a gradually increasing huskiness of the voice. Pemberton found that 25.4 per cent of the cases showed definite hyperthyroidism, evidenced by the symptoms and physical examination and corroborated by an increased basal metabolic rate. He also remarked that the pressure symptoms are not dependent on the size of the tumor but on its location and the degree of compression.

On examination a few cases have been found in which the growth became so large that the manubrium of the sternum was displaced forward. Dilated veins on the chest wall and neck, due to venous obstruction, are seen in about 10 per cent of the patients. Laryngeal examination will show partial or complete paralysis of one or both cords in about the same proportion of cases. Percussion of the growth is possible in some instances, but the roentgenogram and fluoroscopic examinations give the most accurate location of the tumor.

Malignancy and tuberculosis of the thyroid; thyroiditis.--While tuberculosis of the thyroid does not properly belong under a discussion of goiter, it must be considered, because of its diagnostic importance. Mosiman in 1917 drew attention to the striking relationship between hyperthyroidism and tuberculosis of the thyroid. Plummer and Broders in agreeing with this assertion suggested that either a hypertrophic gland is rendered more susceptible

to invasion by the tuberculosis bacillus or the infection stimulates the parenchyma to an abnormal activity and is thus indirectly responsible for the hyperthyroidism with its attendant symptoms. In a series of seven cases, which they reported, the condition was not diagnosed previous to operation. Since the publication of their paper, however, Dr. Plummer [15] has observed cases in which his diagnosis of tuberculosis was later confirmed by the pathologist. Their classification divides the cases into three groups: I, cases with high degree of hyperthyroidism, II, cases with a moderate degree of hyperthyroidism, and III, cases in which hyperthyroidism was mild or absent. The basal metabolic rates in group I were plus 87 per cent and plus 48 per cent; in group II, plus 26 per cent; in group III, plus 21 per cent. From these figures it may be seen that a severe grade of hyperthyroidism may be present. The authors state that the greater the tuberculous involvement the less severe the toxic symptoms, and this may be explained by the more extensive destruction of the glands. They believe that all cases of tuberculosis of the thyroid are probably secondary to some process elsewhere in the body, but they have been unable to demonstrate the primary lesion in any of their cases.

In considering the differential diagnosis they state that cases of the type placed in group I cannot be differentiated from ordinary exophthalmic goiter. In cases similar to those placed in group III, the condition may at least be suspected before operation. Carcinoma of the thyroid may be associated with hyperthyroidism, but the growth is usually more nodular and is not so apt to involve the entire gland without causing a much larger tumor. Chronic, simple thyroiditis may give the same thyroid signs as tuberculosis, but in the experience of Plummer and Broders has not been associated with hyperthyroidism. Sarcoma and actinomycosis of the thyroid are very rare conditions.

Regarding the prognosis of tuberculosis of the thyroid, Plummer and Broders reported one case was in perfect health two years after operation; one patient had myxedema; three had only recently been operated upon; two had not been heard from.

Malignancy of the thyroid.-- Carcinoma of the thyroid was at one time considered a rare disease, but since our methods of diagnosis have become more accurate, the number of reported cases has greatly increased. In the most comprehensive article on this subject, Wilson reported that at the Mayo Clinic up to January 1, 1921, 10,682 simple goiters and 5,867 exophthalmic goiters had been operated on. Of these 207 (3.5 per cent) were malignant. In addition there were eighty-three inoperable cases in which the diagnosis of malignancy was made. Balfour found the incidence of carcinoma of the thyroid to be 1.6 per cent. He found in a review of 103 cases that 81.5 per cent of the patients were more than forty years of age, but that there were eight cases between the ages of twenty and thirty. Wilson found the preponderance to be in the fifth decade. The latter noted the sex incidence to be 69 per cent in women and 31 per cent in men, about the same as that reported by other writers. He also noted that all but sixty-one of the 290 patients had noticed thyroid enlargement previous to one year before the diagnosis of malignancy. Balfour calls attention to the long history of preexisting goiter as the most significant point from the standpoint of etiology. He points to the fact that in the thyroid as well as in other ductless glands--the thymus, pituitary, adrenal, the spleen, etc.-- cancer very rarely develops within the normal gland. Plummer has said that the disease has never, in his experience, developed in a distinctly and purely hyperplastic gland.

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The diagnosis of carcinoma of the thyroid in the early stages, before the development of the board-like resistance and fixity of the gland,

is extremely difficult. Wilson has said that while a sudden increase in rate of growth of a long-standing, nodular tumor of the thyroid in a patient more than thirty-five is strongly indicative of beginning malignancy, a slow, continuous growth may be almost equally indicative of the same condition. In the series reported by Balfour a positive clinical diagnosis of cancer was only made in 18 per cent. In 36 per cent malignancy was considered as a possibility, while in 46 per cent the condition was not even suspected. The subjective symptoms depend upon which structures are early affected and are usually due to pressure on the trachea, esophagus, larynx and nerves. Coughing and choking spells are of common occurrence. Paralysis of the recurrent laryngeal nerve with consequent change in the voice is often seen. Dysphagia is usually seen in the advanced cases. Pressure on the nerves causing referred pain may be an early symptom. Edema of the trachea may occur early or late. As malignant changes may occur in the substernal and intrathoracic goiters, all the signs and symptoms of these conditions may be present. The general signs of malignancy such as weight loss, secondary anemia, cachexia, etc., appear late in the disease. There may be referred symptoms from metastatic deposits in the liver, lungs, brain or bones.

In considering the differential diagnosis in the early cases one must attempt to differentiate between the benign adenomas and cancer. This may be very difficult because it may be almost impossible to palpate the tumor through the muscles and thyroid tissue. As the surgeon and even the pathologist often have great difficulty in differentiating between the two, it is advisable to remove all tumors of the thyroid gland after the age of twenty-five unless there is some special contra-indication. Chronic simple thyroiditis is usually associated with hypothyroidism and may cause trouble in differentiating from malignancy. This will be considered in detail under the paragraph on thyroid-

itis. The hyperthyroidism usually accompanying tuberculosis rules out carcinoma.

Thyroiditis.--- Bacterial thyroiditis is caused by the settlement of the microorganism itself in the thyroid; toxic thyroiditis is due to the inflammatory reaction of the thyroid when in contact with chemical poisons or microbic toxins in the blood stream.

Although the presence of bacteria had not yet been proved, Kocher believed that acute thyroiditis resulted from the extension to the gland of some infectious organism located elsewhere in the body.

We now know that infection of the thyroid gland may be brought about by several ways as, by direct inoculation, by contiguity, and by a metastatic process through the blood stream. It may occur as a sequela of an acute infectious disease. It may complicate in inflammatory rheumatism, pneumonia, influenza, typhoid, malaria, erysipelas, pharyngitis and tonsillitis.

The diagnosis may be made by finding a hard tumor in the neck. There is history of acute onset. The region of the thyroid is swollen, tense, hot and tender. The patient complains of pain and a feeling of constriction in the neck. There may be involvement of the laryngeal nerves. The cardiovascular symptoms are characteristic. The pulse is out of proportion to the temperature and may beat 140 or more. There is distressing palpitation. Blood pressure is lowered. Pain is accentuated during the movements of the larynx.

This condition must be diagnosed from hemorrhage, in which the symptoms are usually more acute and severe, and from malignancy in which the physical findings are usually characteristic and the history more prolonged.

Woody thyroiditis is a condition that on examination appears to be malignancy. In this condition the trachea, esophagus, thyroid and all the muscles form one hard mass. The larynx does not move up and down on deglutitation since it is immobilized. Besides being extremely hard, its surface is

regular in comtrast to carcinoma. The history also differs in that it is usually of short duration. Severe dyspnea may occur early. The thyroid region is often painful and tender. This condition is more apt to occur in younger patients than is malignancy.

Syphilis, Parasitic thyroiditis, and Hydatid cysts and other lesions of the thyroid gland are too rare to discover consideration in this brief survey.

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Relation of the Basal Metabolic Rate to Diseases of the Thyroid Gland.

As the art of correct diagnosis is the greatest achievement of the true physician; any methods that he may employ to perfect his diagnosis are of value. Next to the roentgen-ray the basal metabolic unit probably ranks as the newest and most valuable diagnostic aid. Like the roentgen-ray, however, its value depends upon the personal equation of the technician, the accuracy and dependability of the apparatus, and the experience of the interpreter.

As in the early days of the roentgen-ray the market is flooded with all kinds of apparatus, so that the different units are reporting widely varying results on the same cases. This undoubtedly has served to discredit the value of the readings in the minds of many prominent surgeons, and it merely serves to emphasize the very great importance of the test being made as scientifically accurate as possible. For clinical work the gasometer method introduced by Tissot in 1904 is most accurate and satisfactory, provided the technician is properly trained. Under such conditions the chance for technical error is reduced to less than one per cent.

Only a few years ago studies in metabolism were confined to the experimental stage. Now through the efforts of Lavosier, Atwater, Benedict, DuBois, Plummer, Boothby, Sandiford and others, metabolic studies form an important branch of clinical medicine. Lavosier was the first to point out that all life processes are those of oxidation with the elimination of heat. An apparatus to accurately measure the gaseous exchange between a living organism and the atmosphere which surrounds it, while at the same time measuring the quantity of heat produced by the organism, was first successfully constructed by Rubner. The efforts of Atwater, Benedict and DuBois carried the work from the experimental to the practical stage. The clinical application of the

unit with attendant studies especially in diseases of the thyroid has been largely the work of Plummer and his assistants, Boothby and Sandiford.

For convenience basal metabolic rates are expressed in percentages of the normal. When the heat production is greater than normal, it is plus, when less than normal, it is minus. The term basal is used to indicate that the test was made at a time and under such conditions that the rate obtained would be uninfluenced by such factors as exercise and digestion, both of which ordinarily increase the rate a few points. Hence the test is made as a rule at 8 A.M. when the patient has been without food for twelve hours and for one-half an hour before the test is taken the patient is kept lying down and at complete rest, thus insuring muscular inactivity and giving the basal or minimal heat production.

Clinical interpretation of results.-- For clinical purposes a rate of between minus 10 per cent and plus 10 per cent is considered normal. As a rule little clinical significance is attached to a rating of plus 15 per cent, especially at a first test when the nervous apprehension of the patient and attendant muscular activity may have to be considered. A second test without these vitiating factors being present often shows a plus 8 per cent or plus 10 per cent rate. Above 15 per cent there is a proportionate degree of significance attached to a reading as the rate rises. In some cases the rate may go as high as plus 140 per cent, but it is the exception rather than the rule to see metabolic readings above plus 100 per cent. Such a rate is occasionally seen in cases of markedly toxic goiter with rapid loss of weight. The opposite condition is found in myxedema, where there is a markedly deficient oxidation or metabolism, and the rate may drop to minus 40 per cent or lower.

The metabolic rate, then, is an index of the rate of oxidation

going on in the cells of the body, and just as by the aid of the clinical thermometer we may classify diseases as febrile or afebrile, so with the metabolic unit we may make a classification of hypo- and hyper-oxidation diseases.

In considering its relation to diseases of the thyroid gland, the metabolic unit is valuable for its negative findings. It is just as important to find a normal metabolic rate in a suspected case of hyperthyroidism, as it is to obtain a high rate in a case of exophthalmic goiter. Young, highly neurotic girls, who are underweight, and who complain of a rapid heart, palpitation, tremor, etc, and who present a symmetrical enlargement of the thyroid gland, with thrills and bruits, often furnish a difficult diagnosis. The establishment of a normal basal metabolic rate in these cases at once eliminates the possibility of hyperthyroidism and surgery.

The relation of the basal metabolic rate to exophthalmic goiter. -- The metabolic rate is of great importance in exophthalmic goiter, and yet it is a common mistake to consider the rate as an index of the patient's ability to undergo operation. The rate should merely be considered as one of several factors including the history of recent or impending crisis, the physical findings, especially the weight and strength records, the condition of the heart, etc.

There are still many factors regarding metabolism in this disease which we do not thoroughly understand. Some individuals are able to carry a rate of over plus 100 per cent for several months with greater ease than others whose rates are not over plus 60 per cent. While the high rate may persist over a long period of time in some, in others it falls rapidly to normal in a few weeks. The disease naturally progresses by a series of crises, so that if a curve be made to represent the degree of hyperthyroidism, it may gradually rise until it reaches the highest point shortly before the end of the

first year, as has been shown by Plummer. During the second year there may be two or more crises which, if the patient lives, may result in permanent myocardial and renal degeneration with a progressive failure in health. Aside from the occasional case of spontaneous cure a considerable number slowly improve, but the majority never regain their normal health. The time and number of the crises may show marked variation. Plummer has emphasized the point that operation should never be made while the curve is rising but only after the peak is passed and the metabolic rate is stationary or falling. In general the rate rises in proportion to the degree of hyperthyroidism, yet it is not uncommon to see a lower reading in a patient approaching a crisis than in one who recently passed through this stage. The operative risk would be far less in the latter condition. In considering the advisability of operating upon a case of Grave's disease we should look upon the metabolic rate as merely an aid and not the deciding factor in selecting the right time for operation. A rising pulse curve, while of less importance, should be considered. It is usually safer to operate when the curve is stationary. Considerable progressive rapid loss of weight indicates a poor surgical risk, especially when primary thyroidectomy is considered, but even the simple operation of ligation under local anesthesia is attended with considerable risk when a crisis is approaching. Vomiting, diarrhea, and anorexia warn of a crisis and should be given more consideration than a low metabolic rate. Loss of strength or muscular asthenia as a diagnostic sign in Grave's disease is most important but has received less consideration than it deserves. As a rule the patient who is unable to walk is in no condition for operation.

We are indebted to Plummer for a very simple and dramatic test of the degrees of muscular asthenia present--the quadriceps test---having the patient mount a step without holding onto a support. The patients with true hyperthyroidism usually hesitate or falter and instinctively seek some means

of support or in advanced cases are incapable of mounting the step, whereas the pseudo cases usually have no difficulty in quickly performing the test successfully.

During the first few weeks of incipient Grave's disease with a moderate loss of weight and strength and a metabolic rate below plus 50 per cent and a regular pulse not over 140 and slight or no dilatation of the heart, the operation of primary thyroidectomy may be performed with only moderate risk. The determination of the metabolic rate in these cases is especially valuable as an index of the degree of hyperthyroidism. In more advanced cases the graphic metabolic curve in conjunction with the other factors is often an aid in determining the opportune time to perform ligations and later thyroidectomy.

The metabolic rate in relation to adenoma with hyperthyroidism. -- The basal metabolic rate is of greatest importance in dividing adenomas of the thyroid into those with hyperthyroidism and those without hyperthyroidism. While in the majority of cases it is possible to do this clinically, the metabolic rate clears up the diagnosis beyond a doubt. It is especially valuable, however, to the physician who sees only an occasional goiter patient. It is true that a few patients are seen in both the exophthalmic and adenoma classes whose metabolic rates are normal because the hyperthyroidism is in a quiescent state.

When compared with adenoma with hyperthyroidism, exophthalmic goiter causes a train of acute symptoms. In the majority of instances symptoms of hyperthyroidism do not develop until from fifteen to twenty years after the appearence of the adenoma, but persist for three and one-half years before the patient consults a surgeon. Consequently the damage to the cardiac, arterial and renal systems is more serious and permanent than it is in exophthalmic goiter. The metabolic rate, of course, does not furnish an index to the condition of these

symptoms and is, therefore, of much less value than in exophthalmic goiter where this damage is not as important a factor as is the degree of hyperthyroidism. In adenoma with hyperthyroidism the surgeon is not concerned as much with the possibility of post-operative hyperthyroidism as with the ability of the heart and kidneys to properly functionate.

The average metabolic rate in adenomas with hyperthyroidism as shown by Boothby[12] is plus 35 per cent, while in exophthalmic goiter the average is over plus 50 per cent. It is uncommon to see the metabolic rate above plus 35 per cent in adenomas, while in exophthalmic goiter the range varies widely from plus 15 per cent to plus 140 per cent.

The metabolic rate clearly indicates the success of operative methods in the treatment of adenoma with hyperthyroidism as shown by Judd in a series of cases in which the pre-operative rate was plus 32.7 per cent, and the average post-operative rate was plus 9.2 per cent. These figures are in accord with those of Boothby,[12] who found that in 67 per cent of the cases the rate returned to normal within two weeks after operation. Plummer has pointed out that thyroidectomy in these cases almost immediately cures the patient. Boothby[12] showed in marked contrast with this type a severe group of exophthalmic goiters in whom the average pre-operative rate was plus 66 per cent. These patients were subjected to rest in bed and two ligations at an interval of a week or more, and within ten days after the second ligation the rate was plus 50 per cent. After three months' rest at home these patients had an average rate of plus 42 per cent, with corresponding clinical improvement; within two weeks after thyroidectomy the rate had dropped to plus 19 per cent, but in only 36 per cent did it return to normal in this time.

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Pathological Classification of Goiter.

MacCarty, in 1912, divided goiters into two pathological groups, namely:

"A group composed of symmetric thyroids and a group of assymetric or nodular thyroids.

"The symmetric thyroids vary in size from that of a normal fetal thyroid to many times the normal. Upon gross examination of the cut surface of the symmetric specimen two very definite pictures are noted, namely, meaty glands with acini which are not distended and hence not readily visible, and glands consisting of large acini, which are filled with jelly-like colloid material. These are, however, descriptions of the extreme conditions, because many specimens, though meaty, also contain some colloid material."

Based on the clinical classification used in this paper, the first of these descriptions would be applied to cases of exophthalmic goiter, and the second to adolescent colloid goiter.

MacCarty further stated, "The microscopic examination of these glands reveals varying pictures of the acini, or gland units. The extremes of these are small acini with epithelial hyperplasia without colloid and large acini with colloid and no epithelial hyperplasia. Both epithelial hyperplasia and intra-acinar colloid are, however, often present in the same gland."

Under the normal shaped or symmetric thyroid he described, "The fetal thyroid, the glandular unit, or acinus, of which is a group of cells without a patent lumen. The normal adult thyroid is composed of acini, which consist of low or flat cuboid cells, with a small amount of protoplasm, surrounding a lumen, which is filled with a colloid substance. One also occasionally finds an adult thyroid which contains, in addition to the colloid acini, many acini of the fetal type.

"Where the 'normal' thyroid ceases to be normal and begins to be pathologic is still undetermined... the hypertrophic thyroid consists of large colloid acini;...(and) the hypertrophic thyroids with epithelial hypertrophy or hyperplasia without intra-acinar colloid, (is) a condition which is definitely associated with a certain symptom-complex which we call hyperthyroidism.

"Assymmetric or nodular glands contain usually, if not always, one or more encapsulated oval or round adenomas. These vary greatly in size and number..... The capsule of the adenoma is fibrous connective tissue, which varies greatly in thickness and density. It is frequently calcareous. The body of the tumor upon gross section is variable. The cut surface of the simplest undegenerated tumor is firm, uniform, and free from macroscopically visible colloid. The acini of such a tumor are fetal in type, although they may contain a very small lumen. The acini are more widely separated by a delicate interacinar stroma than in the fetal thyroid. Upon the cut surface one readily recognizes that one does not always find the simple adenomas which have just been described; colloid material is frequently seen in large amounts; such acini are easily grossly visible. Upon microscopic examination the acini are found to be large, lined with flat cuboid cells, and filled with colloid. The colloid acini are indistinguishable from those found in colloid thyroids. If one searches such a tumor, fetal acini are certainly to be found. Acini composed of hypertrophic cells are occasionally found.

"Red, brown, or old yellowish hemorrhagic areas are often found in these tumors. Areas of dense and even calcareous tissue are also frequent. Many tumors are found in which a part or all of the tissue within the capsules has become liquefied. The contents of such a degenerative cyst have an amber color or are hemorrhagic. They practically always contain cholestrin crystals.

"The surrounding gland in which these tumors are present, presents the same acinar characteristics which have been described above for the symmetric thyroids. In the majority of specimens the surrounding gland is composed of the colloid and fetal acini."

Under the classification of clinical groups used in this paper the adenomas with and without hyperthyroidism would correspond to the assymetric or nodular tumor as described by MacCarty.

Wilson[3] in 1908 pointed out that there were two distinct types of glands to be found among thyroids removed from toxic goiter cases. He indicated that the essential element in a large percentage of the cases was an increase in the amount of working tissue--parenchymalcells-- within the previously formed acini, or, in other words, hypertrophies, hyperplasias, and regenerations, while in a smaller percentage of the cases there was an apparent increase in the amount of working tissue--parenchyma, due to an increase in the number of acini, or in other words, adenomas, adenomatoses, etc. Class I, containing the hypertrophies, hyperplasias, and extreme regenerations, constituted 79 per cent of the total number of specimens examined, while Class II, containing the fetal and colloid adenomas, the adenomatoses, and the so-called simple colloid thyroids, constituted 21 per cent of the specimens examined.[4]

In 1913 Wilson[5] stated:

"Our knowledge of the clinical, toxic, non-exophthalmic type is still too incomplete to permit us to draw conclusions concerning the details of their pathology." Again[7], "The pathology of toxic non-exophthalmic goiter is one of increased parenchyma through regenerative processes in atrophic parenchyma, or the formation of new parenchyma of the fetal type, with an increase in each instance of secretory activity and of absorption."

Pathology of Malignant Tumors of the Thyroid.

Owing to the great variation in the histology of the tumors and the similarity between the benign and malignant tissues, there has been a wide discrepancy in the pathological classification of malignant tumors of the thyroid. There is no generally accepted classification. Tumors that appear to be benign to some pathologists are called malignant by others. There are few pathologists who have not been forced to change their opinion on some cases.

Wilson[8] says, "Adenomas are due to circumscribed proliferation of (usually embryonal) parenchymatous tissue. If these adenomas remain perfectly encapsulated and if they cease to proliferate and gradually degenerate they are 'benign', in the sense that they do not invade surrounding structures and do not metastasize... If adenomas continue to proliferate rather than to degenerate they may penetrate their capsule, invade, and metastasize. These proliferating adenomas thus may or may not be malignant and histologically it is almost impossible to differentiate the two. Broadly speaking, the only reliable marks of distinction are the details which indicate the preponderance of one or the other of the two processes, namely, proliferation and differentiation. Again, broadly speaking, it follows from this, that any sizable adenoma of the thyroid composed of embryonal tissue in a person of cancer age which histologically shows that it is in active proliferation is potentially malignant even though it is still contained entirely within its capsule.....

"Neoplasms of the thyroid composed of adult parenchymatous cells, if encapsulated, always suggest having been derived from embryonal tissue during prenatal life though by no means can this always be proved.... Such encapsulated masses of large adult parenchymatous cells, while frequently arranged in acini resembling those of the normal thyroid, are more frequently the subject of extensive degeneration.... The epithelial cells adjacent thereto are large, often with hydropic cytoplasm and relatively small nuclei. The parenchyma is

not infrequently markedly papilliferous.... They are undoubtedly the origin of that group of malignant tumors usually designated adenocarcinomas... Solid homogeneous non-functionating aberrant proliferations of the thyroid are almost always neoplasms which invade surrounding structures and metastasize to distant organs....

"All other tumors of the thyroid associated with symptoms of malignancy are usually described as sarcomas. Beside their connective tissue elements in which any form of sarcoma cell may be the dominant one, although it is most frequently the spindle-cell type, there are also almost invariably present large or small groups of parenchymatous cells which show that they are also proliferating."

Pathological Picture of Tuberculosis of the Thyroid. -- Plummer and Broders found various pathological pictures in the series of cases which they described under Tuberculosis of the Thyroid. These pictures were alike, however, in that all but one showed parenchymatous hypertrophy. Some showed extensive tuberculosis, while fibrosis and round cell infiltration were present in various degrees. The glands were hard, somewhat fixed, and nodular.

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The Medical Treatment of Goiter.

Less than a decade ago the majority of physicians in this country favored the medical treatment of goiter. The excellent results obtained with surgery by such men as Mayo, Crile, Halsted, Ochsner, Crotti and others has now largely changed this view. In fact, there has been a dangerous tendency on the part of some surgeons to go to the other extreme, and through inexperience or ignorance even colloid adolescent goiters have been removed.

It has been proved beyond a doubt by the statistics of large surgical clinics that there is no comparison in the results obtained by the medical and the surgical treatment of goiter. Moreover, with improved methods of surgical technic the operative risk has now been reduced to almost a negligible factor except in the very toxic cases. At the same time no conscientious surgeon will deny that medical treatment is indicated in a certain number of goiter cases.

Medical treatment is indicated in the following types of goiters:

The colloid goiter seen at the age of puberty.

Simple goiter causing no obstructive symptoms in persons under twenty-five years of age.

The compensatory hypertrophy of the gland during pregnancy and menopause.

Cases of marked hyperthyroidism in which the risk is such as to contra-indicate immediate operation.

Cases in which the operation cannot be attempted with a fair degree of safety.

<u>Colloid goiter</u> responds the most favorably of all forms to medical treatment. It is this type of goiter which has been called the physio-

logical compensatory hypertrophy of puberty. The thyroid gland enlarges in a compensatory manner because it is unable to meed the demands for iodin made upon it by the growing body. At one of our large universities this condition has been observed in varying degree in 60 per cent of the women students.

The work of Marine in preventing the development of this condition by feeding iodin to several thousand school children in an Ohio city is now considered a classical experiment. Some authorities have stated that in time we will have iodin on our tables and use it as we now use salt as a prophylactic measure against this form of goiter. The idea is not a new one, however, as back in 1200 Rober von Salerno was using toasted sponges, toasted egg shells, and corals as treatment for goiter. It was the Swiss physician, Coindet, in 1829, who was the first to use iodin as a therapeutic measure against goiter. Since that time the use of iodin has become very common and it still is the only specific treatment we have for simple goiter.

Just what action iodin has on a colloid goiter is still a question. Crotti believes its action to be two fold, namely: (1) Iodin activates the functional activity of the epithelium, and accelerates the liquefaction of the colloid. (2) It acts as an antiseptic.

Iodin may be administered in several forms. The old method of painting the goiter has long since been discarded because it blistered the skin and made an unsightly appearance. Externally it may be administered in the form of an ointment, and Crotti has suggested the following formula:

R_x Kal. iodat . . . . . 10 grains

Aq. dist. . . . . 10 "

Lanolin . . . . . 30 "

Vaseline . . . . . 70 "

Tinct. of iodin xxx drops.

It makes no difference what part of the body is rubbed, so long as the iodin is absorbed. Because of the psychological effect of applying it on the goiter, however, patients are more apt to follow the treatment faithfully if they think the medicine attacks the goiter directly.

Internally iodin may be given in the form of a saturated solution of potassium iodid in doses of ten drops twice a day. If preferred, syrup of iodide of iron may be used.

The use of thyroid extract is not recommended, nor is the use of roentgen-ray or radium, since the purpose of medical treatment is not to destroy the overworked gland but merely to relieve the excessive demand upon it.

Probably the most wonderful work that has been accomplished in the medical treatment of goiter is that done by Plummer. With thyroxin he has caused large colloid goiters to disappear within a few weeks, and some of his cures have indeed been marvelous.

Rest and proper hygiene are of course essential in the successful treatment of colloid goiter. Providing there are no pressure symptoms and the goiter is not rapidly enlarging, or is markedly disfiguring, surgical treatment should not be considered until the patient is at least twenty-five years of age. Many of these goiters will disappear spontaneously, others will respond to medical treatment, and as Mayo has said, some will be cured in spite of treatment. Sistrunk says that its failure to disappear under the administration of iodin and thyroxin probably indicates that it is not a simple colloid goiter but one of the mixed types often seen, in which a colloid goiter is associated with small adenomatous growths of the thyroid. When such goiters are treated with iodin and thyroxin the colloid portion disappears and the goiter is reduced in size, but the adenomas remain and are then more easily recognized. Colloid

goiters may recur when removed surgically unless iodin or thyroxin is administered as a postoperative measure.

Purely colloid goiters are very rarely seen after thirty years of age and a careful examination will usually reveal one or more adenomas. The finding of an adenoma may be considered as an indication for surgery.

Simple adenomatous goiter.-- Unless causing undue pressure, marked disfigurement, or toxic symptoms this type of goiter had best be left alone until the patient is twenty-five years of age. It is rarely toxic before the person has reached the age of thirty. Toxic symptoms, however, are frequently brought on by the use of iodin, which should never be administered to these cases. After twenty-five or thirty years of age a partial thyroidectomy may be considered for the following reasons: the thyroid gland is no longer as essential to the body development of the individual; it may be desirable to remove the goiter for cosmetic purposes; the goiter may be enlarging rapidly and be causing pressure symptoms; it should be removed to safeguard the individual against the later development of toxic symptoms, since about one in every four adenomas later become toxic. Roentgen-ray and radium are not recommended.

Compensatory hypertrophy of the gland during pregnancy and menopause.-- The treatment of this condition should be the same as that for colloid goiter. One should be sure that the condition is purely compensatory and that a true toxic goiter is not developing. The basal metabolic rate is of value in confirming the true diagnosis.

Cases of marked hyperthyroidism in which the risk is such as to contra-indicate immediate operation.-- Mayo has said that exophthalmic goiter should never be considered an emergency operation. Cases that are on the verge or are already in a crisis should be considered as medical. The experience of the surgeons at the Mayo Clinic is that any operation at this time is attempted with grave risk. With a raging metabolism and a dilated heart the indications

are for rest in bed, fluids, digitalis and quiet. The detailed treatment of this condition will be considered in the chapter on Preoperative Treatment. The case should be considered medical as long as the metabolic rate is rising and the heart dilated or decompensated. Many factors, that will be discussed later, must be considered before the patient may be judged fit for surgery. This is the time to consider roentgen-ray and radium treatment.

The value of roentgen-rays and radium in the treatment of goiter has not been definitely determined. Plummer and Mayo, Crile, Crotti, Ochsner, and many other men prominent in goiter work are not using roentgen-rays and radium except in certain cases. I observed a large series of cases in which Plummer tested this manner of treatment. The results were disappointing in so far as therapeutic value is concerned, but as a palliative measure they proved satisfactory. For a few days following the treatments there would be a slight improvement accompanied by a drop of ten to twenty points in the metabolic rate. Then the rate would rise again, in some cases higher than before treatment, and the symptoms would return as before. The treatments, however, served a certain definite purpose in that they kept the patient's mind occupied and assured him that something was being done to better his condition. At the same time quinine hydrobromide, quinine-urea or hot water injections into the goiter and other similar methods are used to tide the patient over until surgery may be safely attempted.

Lower and Crile say that roentgenologic treatment does reduce the activity of the thyroid. It is a simple painless procedure. They believe it has the following disadvantages: The dose required to produce a given effect is at best a guess; relapses are common; the delay in unsuccessful cases leads to serious damage to certain organs--the myocardium, liver, nervous system, etc.; in cases of operation later, the scar tissue and adhesions caused by the roentgen-ray are a handicap. The dilemma in the use of the roentgen-ray is: myxedema

or relapse. If the dose is sufficient to kill all the thyroid cells, myxedema results; if the dose does not kill the cells, they recover and there is relapse.

Nichols of the Cleveland clinic, Means and Aub of Boston, Stoney, Lange, Pfahler, Boggs, Hubeny, Grier and many others have reported excellent results with the use of roentgenologic treatment in goiter. Dr. Nichols told me that he has had definite results in the treatment of exophthalmic goiter. He governs treatment by the metabolic rate, and believes these cases should receive the same advantages in pre-operative care as are given surgical patients.

Hubeny has said that the roentgenology is not to supersede surgery but is preferred in many cases because the percentage of cure is as great. The technic of his treatment is as follows: Use an interruptless machine, and a broad focus Coolidge tube. A parallel spark gap of nine inches. The rays are filtered through 4 mm. of aluminum and 1 mm. of leather. The skin focus distance is eight inches. Three areas are treated--the right half of the goiter, the left half, and the thymic region. Each area receives two-thirds of an erythema dose. The treatment is repeated in three weeks and then stopped for three months. This is considered as one series. He considers this as technic #1. A second technic is similar except that the right and left posterior cervical ganglion areas are treated. Technic #2 is one of choice when the patient is not highly toxic, permitting a gradual recrudescence of symptoms with less tendency toward recurrence. The area over the cervical ganglion is included, based on the observation of Cannon that stimulation of these centers causes secretory activity in the thyroid, while conversely the effect of roentgen-rays seems to inhibit their action. If immediate results are desired, as in cardiac debility or marked thyro-toxicosis, technic #1 is to be employed.

Favorable signs are abatement of nervous symptoms, gain in weight, slowing and stabilizing of pulse, and lessened, or disappearance of exophthalmos, in 40 per cent of cases. The goiter may not decrease in size.

The first treatment may increase toxemia to a dangerous degree. To guard against this, start with small doses and precede this with rest in bed.

Cases in which operation cannot be attempted with a fair degree of safety.-- There are a few cases in which the risk is such as to preclude operation. Examples are toxic adenomas of long standing in which there has been serious damage to the heart and kidneys, intrathoracic goiters of a similar type, malignant growths too extensive to be removed.

Conditions such as these must be considered beyond the realm of surgical relief and should be made as comfortable as possible by medical means.

Before concluding the subject of medical treatment of goiter, a final word of warning regarding the indiscriminate use of iodin may be given. Iodin used over too long a period of time, or in too large doses, may give rise to the classical symptoms of intolerance, such as salivation, watering of the eyes and congestion of the mucous membranes as well as severe symptoms of hyperthyroidism.

In summarizing the medical treatment of goiter from the standpoint of the internist Lichty[6] believes attention should be directed to the following factors: Disturbance of the nervous mechanism must be overcome by nerve sedatives (based on Cannon's work); loss of weight must be overcome by increased food intake (based on the metabolic studies of Du Bois); disturbances of certain secretion must be treated by medication (based on Marine's work); there must be proper rest (based on the work of Weir Mitchell).

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Preoperative Treatment of Exophthalmic Goiter and of Adenoma with Hyperthyroidism.

There exists considerable difference of opinion regarding the preoperative treatment of exophthalmic goiter and adenoma with hyperthyroidism. Plummer maintains that in the former condition the disease progresses by a series of waves or crises and that operation should never be attempted while the wave is rising or at the crest. Crile states that he operates on all cases within one week after they are admitted to the hospital, providing they are properly digitalized and the kidney function is within normal limits. His contention is that the disease is in an active progressive state and that immediate operation will check this progression and prevent further damage. Other men maintain that the foci of infection should first be eliminated and the severity of the disease lessened by such therapeutic agents as radium and the roentgen ray. Crotti states that the preliminary treatment may last only a few days, or several weeks, depending on the individual case.

It is obvious that before considering the matter of treatment, it is necessary to establish a correct diagnosis. There should be an examination of the vocal cords in all cases. If there is a preoperative paralysis of one vocal cord, injury to the other cord at the time of operation will produce serious consequences. Roentgenological examination of the chest should be made in cases of adenoma to rule out the possibility of a substernal goiter. The basal metabolic rate, blood pressure, pulse, and temperature should always be taken. In long-standing cases of exophthalmic goiter and of adenoma with hyperthyroidism the renal function must be ascertained.

Personal supervision of the case is important. Probably in no other disease is the nervous system so keyed up as in exophthalmic goiter. Cheerful, quiet, gentle attendants are essential. A sunny room helps to tide

over the periods of depression. A crisis may be precipitated by sudden, noisy entrance into the patient's room. Visitors, the house and nursing staff should know that these patients are extremely irritable and sensitive, and that one should never attempt to chastise or argue with them. Complete cooperation of the patient must be obtained by exercising the greatest diplomacy, tact and thoughtfulness. His fears should be quieted; his wishes granted as far as possible; he should be humored and his mind kept so occupied that he has no time for reflection. A few kind words will often allay worry over some trivial matter which to him is very grave. Such measures will be found far more effective than drugs in reestablishing the patient's self-confidence and in quieting his nervous system.

These cases should never be placed in wards where they may be greatly disturbed and annoyed by other patients, nor should two such cases be placed together. The more emotional one will upset the other. To overcome insomnia the bed should be comfortable. Even the selection of pictures and the color of the furnishings of the room should be such as to induce a quieting and restful influence.

Unless in a crisis or in an extremely weakened condition, patients should be allowed to use the toilet, and after a few days' rest in bed permitted to sit in a chair for a short time twice a day. A young person constantly confined to bed becomes restless and thrashes about until his extremities are chafed and his nervous system upset. An older person weakens and loses his appetite. After a preliminary rest period, the length of which is governed by the patient's condition and a study of the metabolic rate, Plummer encourages his cases to be up and around the room a little more each day until their strength will permit them to walk up and down the halls without tiring.

Crotti considers menstruation a contra-indication to operation, as the nervous system of patients is often very much disturbed during the menstrual cycle. He believes it is better to wait until that process is over.

Preoperative therapy. -- With the exception of digitalis, drugs are of little value in the preoperative treatment of toxic goiter. Plummer digitalizes all cases having cardiac dilatation, or myocardial degeneration as evidenced by auricular fibrillation, or edema of cardiac origin. Other men routinely digitalize all cases of goiter having hyperthyroidism, as well as simple goiters when there is myocardial damage. The tincture of digitalis minims XXX may be given every four hours for fifteen doses, and if necessary this is repeated. His cases are operated upon as soon as the heart is digitalized as he claims there is then a maximum effect of the digitalis which is not sustained.

Plummer uses the tincture of digitalis in doses of c.c.I to c.c. II t.i.d. by mouth, the amount depending upon the individual case. It is stopped when the patient complains of nausea and anorexia and before the onset of vomiting. Thirty cubic centimeters is usually sufficient. Plummer is not insistent on immediate operation once the case is digitalized, but considers the effect of the digitalis lasts over a period of from two to three weeks.

Bismuth sub-gallate in doses up to 60 gr. a day gives the best results in checking the diarrhea which is frequently severe during a crisis. Calomel and opium pills t.i.d. are also effective.

Insomnia and restlessness are difficult to control. Opiates are objectionable because they irritate the already highly sensitive gastrointestinal tract, and their use is required over too long a period of time. Occasional small doses of codeine may be required. Veronal in 5 to 10 gr. doses is often satisfactory. The bromides may help, but as a rule are only effective in large doses and are then objectionable because of a tendency to cause gastric disturbances.

Vomiting during a crisis cannot be controlled by drugs. A dry diet consisting only of crackers, toast, or bread should be tried. Fluids

must be supplied by the rectum or subcutaneously. A careful record of the fluid intake and output should be kept. Blood urea and phenolsulphonephthalein tests are frequently indicated. During a crisis the patient's appetite may be as bizarre as that of a pregnant woman. The mere sight of a hospital tray may induce a vomiting spell. Special effort must be made to tempt the patient with something that he craves. It may be wild cherries or chili con carne.

During the intervals between crises when the patient usually has a ravenous appetite, special provision should be made for him to have lunches and second servings. Tea and coffee are prohibited because of their stimulating tendencies. Crotti advocates giving the patient 150 gm. of glucose and 5 to 10 gm. of bicarbonate of soda as a preventative of postoperative acidosis.

An ice bag is applied to the heart when the pulse is over one hundred, and when the rate is very rapid or there is fever, an ice cap may also be used.

Cathartics, except an occasional small dose of magnesium sulphate or one of the mild laxatives are contra-indicated. As the gastro-intestinal tract is already in an irritated state, a spell of diarrhea may be induced by cathartics.

There should be a record of the pulse, temperature, and blood pressure, bowel movements, and the daily intake and output of fluids. Patients should be weighed at least once a week if possible, and a weight curve charted. A curve of the metabolic rate is convenient. The pulse pressure is an important factor to bear in mind.

Although the use of roentgen rays, radium, quinine-hydrobromide, etc., does not appear to produce any permanent beneficial effect, still for their temporary action and as a means of keeping the patient's mind occupied there is some benefit to be derived from their use.

The preoperative directions as used at the Mayo Clinic are simple. The condition of the patient having been previously tested by hot water injections or ligations, if indicated, and operation having been determined upon, he is informed at least one day in advance of this determination, and his complete confidence gained. The best assurance that he has is gained by contact before entering and while in the hospital with the postoperative cases. This intermingling of the patients and their friends is bound to occur and as Percy has pointed out in criticism of Crile's anoci-association plan, "these patients tell each other beforehand concerning the method each surgeon is in the habit of employing, so that they are fully informed about this mystery." There are, however, many valuable ideas in the Crile method of treatment that may be applied from his rules, which are as follows:

I-Introducing the patient to hospital activities:

1. All accommodations are arranged before the patient enters the hospital.
2. Patient is passed without delay to her room which is made as comfortable and homelike as possible.
3. The patient is to remain in bed continually.
4. Visitors, house and nursing staff never mention operation, but give assurance that patient will be entirely well.
5. No formal history or examination until patient is tolerant to surroundings.

II-Examination, Tests and Therapy:

1. Thorough history and physical examination, especially of the heart. Care taken not to tire or upset the patient.
2. Metabolism test to determine the increase in body metabolism.
3. Adrenalin sensitization (Goetsch) test.
4. Phenolsulphonephthalein and Mosenthal nephritic tests.
5. In cases of myocarditis, tachycardia and edema, Tr. digitalis minims XXX every four hours for fifteen doses is given and repeated if necessary.
6. Sodium Bromide gr. XXX every night.
7. Dessicated thyroid extract gr. ll the night before and morning of operation.

III Preoperative routine:

1. The following measures are carried out two to four days before the operation.

2. Operating room clothes on patient continually.
3. Sterile hypo given at 8:00 A.M. every day.
4. Inhalations of nitrous oxide and oxygen in room at 9:00 A.M. every day. These are explained as being given for the heart.
5. On day of operation morphia gr. 1/6 and atropine gr. 1/150 by hypo substituted for sterile hypo previously given at this time.
6. Inhalation given as usual in room and patient either operated in bed or taken to operating room under anesthesia.

Undoubtedly gas-oxygen is the anesthesia of choice in a selected group of cases, the same is true of anoci-association, but probably local novocain anesthesia is sufficient in the majority of cases. A fuller discussion of anesthesia will follow under operative treatment.

Some surgeons object to the use of atropine because of its inhibiting effect on the depressor nerves of the heart.

If possible, goiter patients ought to be operated upon in the early morning before mental fatigue has had its effect on the body. All patients are tired at the end of the day and especially goiter patients. The strain of a local operation at such a time is a tax on their minds as well as on the surgeon's.

All unnecessary noise must be eliminated from the operating room, and under ideal conditions the operation is performed with as few persons present as possible. The position of the patient on the table should be made comfortable.

The shorter the time spent in the operating room, the less the trauma and hemorrhage; the more experienced the surgeon and the smoother his team work, the better are the patient's chances of a successful recovery.

Summary of Preoperative Treatment.

1. There exists difference of opinion regarding the method of preoperative treatment. Plummer advocates preoperative medical measures until he believes the patient fit for operation. Crile advocates immediate operation, once the case is digitalized.

2. Treatment is based upon the diagnosis. The routine laboratory examination should include a roentgenological examination of the chest in cases of adenoma, local metabolic rate, and renal tests as indicated. Examination of the vocal cords in all cases is important.

3. Personal supervision of patients with attention to details is essential.

4. Drugs are of little avail, with the exception of digitalis.

5. Anoci-association is valuable in a selected group of cases.

6. Radium, roentgen-ray therapy, hot water and quinine-urea injections are valuable only as palliative measures, and as an index of the reaction of hyperthyroidism.

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The Surgical Treatment of Goiter.

There are several important factors governing the successful surgical treatment of goiter:

Choice of operation (based on the type of goiter).

Choice of anesthesia.

Exposure of the operating field.

Rapid bloodless resection of the gland without injury to the laryngeal nerves.

The proper time to stop an operation.

Proper drainage; packing; primary or delayed closure of the wound.

Postoperative care and treatment of complications.

The preparation of the patient, and the choice and time of operation have been discussed elsewhere. The choice of anesthesia depends upon the experience and personal preference of the surgeon. Years ago Kocher demonstrated the value of local anesthesia, and at the present time this method is favored by many surgeons.

Crile says, "Since all inhalation anesthetics cause suboxidation in extreme cases, deep surgical anesthesia, especially ether anesthesia, is ruled out. Gas and oxygenia analgesia, combined with local anesthesia, is entirely free from this serious objection. Ether anesthesia almost wholly suspends the internal respiration and is especially damaging."

He believes it is important that the "bad risk" patient should be protected against suboxidation, inhalation anesthesia, pain, fear and worry.

In Crile's hands anoci-anesthesia, has been very successful. Other men have not met with the same success with this method. In considering

the remarkable results obtained by Crile, one must consider his wonderful surgical ability and the excellent team-work of his assistants, trained by many years of experience.

There are a number of advantages in using the novocain method of infiltrating the tissues:

The operator and his assistants must handle the tissues most gently and carefully to minimize the sensation of pain and pressure.

Any trauma or injury to the recurrent laryngeal nerve may at once be detected by talking with the patient.

When the operation is finished, undetected bleeders may be found by causing the patient to cough and strain.

The disagreeable postoperative nausea and vomiting from ether is eliminated.

The risk of postoperative hyperthyroidism is diminished.

There is a decreased chance of postoperative aspiration pneumonia, although pneumonia does occur.

The operator can tell whether the patient's condition warrants continuing the operation.

The disadvantages of novocain anesthesia are:

Increased strain on the surgeon.

Increased psychic disturbance to the patient.

Increased time required for operating.

The ideal method is to adapt the anesthesia to the individual case. Some persons will tolerate novocain anesthesia better than others. There is no distinct advantage to be gained, for example, in using novocain alone in order to remove a simple adenoma from a very nervous individual. I believe in the majority of such cases ether anesthesia is indicated. Gas-oxygen is satisfact-

ory but carries more risk for the surgeon, who is not in a position to employ a trained anesthetist. Novocain, combined with a small amount of ether or gas-oxygen, if the patient is very nervous, is successful in the cases of hyperthyroidism. In about 80 per cent of the cases novocain alone will suffice, providing it is properly administered.

When using local anesthesia, one-sixth of one grain of morphine should be given hypodermically about thirty minutes before operation. Many surgeons are using scopalomine successfully, but others believe its use is attended with some risk. For ligation of the superior thyroid vessels about 30 cc.to 100 cc. of .5 per cent novocain solution is required. No adrenalin is used. For a thyroidectomy from 200 cc. to 500 cc. of the same strength novocain is required. It is important to infiltrate the tissues in the superior angles of the neck in order to reach the branches of the cervical nerves. When the gland is exposed more novocain should be injected and this should be repeated from time to time during the operation if there is much complaint from the patient.

The surgeons at the Mayo Clinic feel that the position of the patient on the operating table and the proper exposure of the field of operation are important. The table should be inclined at an angle of about 35^{0} and one or more folded sheets placed behind the neck to give the desired exposure. A goiter screen protects the field from the patient's face. In draping the patient it is well to place wet sterile towels at each side of the neck in order to catch any sudden or unusual hemorrhage that might run down from the operating field.

The preparation of the skin is a matter of individual choice. Whether one merely cleans the skin with soap and water and alcohol or ether, or paints it with picric acid, or a weak solution of iodine, does not affect the ultimate result.

Technic of ligation of the superior thyroid artery.--

A transverse incision two inches long is made in a natural skin crease at the

side of the neck in the region of the vessel. The inner border of the sternomastoid is retracted laterally and the small vessels clamped. The omohyoid muscle is retracted upward and inward with a small curved retractor. This exposes the upper pole of the gland with the superior thyroid vessels. Frequently it will be necessary to ligate one or more branches of the artery. The main vessel can usually be dissected free and a blunt pair of scissors thrust beneath. If the vessel can be easily isolated, two strong artery clamps are applied, the vessels divided, and two ligatures placed one on the proximal and one on the distal side. The clamp on the distal side, the one nearest the brain, should be applied first so that the patient suffers only one sensation of pain. When it is difficult to isolate the vessel, an aneurism needle can be passed beneath it and the vessel ligated. Some surgeons do not isolate the vessel but merely pass two ligatures around the superior poles. The wound may be closed by a subcuticular suture without drainage. Skin clips, silk, or dermal are alternative choices.

Ligation of the inferior thyroid artery.-- This operation has been popular at various times during the past thirty or forty years and at present some surgeons are doing it as a routine. De Quervain is at present probably the strongest advocate for this operation. Penberton and Sistrunk are doing it in selected cases. If following a double ligation of the superior thyroid arteries and a three months' rest cure the patient's condition does not permit a thyroidectomy with a reasonable degree of safety, ligation of one or both of the inferior thyroid vessels may be considered. Owing to some intercurrent disease, or relapse following overexertion on the part of the patient, he may return for thyroidectomy in worse condition than he was previous to the ligation of the superior vessels.

A transverse incision in the same location as the contemplated incision for thyroidectomy is made over the tendon of the omohyoid muscle. The skin flaps are retracted and an incision made along the inner border of the

sternocleidomastoid muscle which is retracted laterally, while the gland is pulled upward and inward. The search for the artery may be difficult owing to its deep location and the proximity of the carotid and other important vessels. Crotti states that the guide for locating the vessel, is the anterior tubercle of the transverse process of the sixth cervical vertebra. One centimeter below this tubercle, as a rule, the inferior thyroid artery is found, its pulsations facilitating the finding of it. With the aid of an aneurism needle a silk ligature may be thrown around the vessel.

This is rather a difficult operation and even for the experienced surgeon, it takes several times as long as to ligate the superior vessels. Undoubtedly it is a useful operation in a few selected cases, but it is unnecessary in the majority of toxic goiters.

Technic of thyroidectomy.-- The most commonly used form of incision is known as the Kocher, and is a low collar incision in a natural skin crease. This incision includes the skin and platysma and extends laterally to the external jugulars. Strong upward traction with sharp retractors is made on the upper flap by an assistant while the skin and platysma is dissected upward about two and one half inches and downward about one inch. A vertical incision is now made separating the sternohyoid muscles and splitting the fibrous capsule of the gland. The index finger is then passed over the surface of the gland separating its attachment to the muscles above. Opinion differs on the necessity of dividing the sternohyoid and sternothyroid muscles. Unquestionably it gives better exposure, and whenever this is required, as in the case of a vascular, friable exophthalmic goiter or a large colloid adenoma, there should be no hesitation about dividing the muscles. The results are the same. The muscles should be divided by placing two Mastin muscle clamps (equipped with special locks to prevent crushing the muscle) transversely across the muscle in the region of the thyroid cartilage. If it does not seem necessary to divide the muscles they may

be retracted laterally with small curved retractors. The sternocleidomastoid can usually be retracted, but should be divided for about one half inch if it limits the working field. C. H. Mayo says that many of the troubles and accidents in the surgery of goiter would be avoided if the preliminary exposure of the thyroid were adequate before proceeding with the gland itself. The skin flaps may be held apart by a self retaining retractor which gives an excellent exposure. The clamps on the upper ends of the muscles may be crossed the one behind the other and then held in place by a single sharp retractor. All bleeding vessels beneath the flaps should be ligated before any attempt is made to remove the goiter, so that the field of operation may not be obscured by hemostats. If there are very large veins on the capsular surface of the gland it is advisable to throw a ligature around them with a small curved needle before proceeding in order to avoid unnecessary soiling and air embolism.

A brief review of the anatomy is now important. The superficial cervical fascia covers the sternocleidomastoid and the prethyroidal muscles which are the sternohyoid, omohyoid, and sternothyroid muscles. The middle cervical fascia forms a sheath for the three thyroidal muscles, and fuses at the midline with the one of the other side and the superficial cervical fascia to form the cervical linea alba. The prevertebral fascia and the middle cervical fascia give rise to the so-called surgical capsule which surrounds the gland. There is a normal plane of cleavage between the sternocleidomastoid muscles and the prethyroid muscles which De Quervain calls the sternomastoid space. There is another plane of cleavage between the prethyroid muscles and the surgical capsule, the sternomuscular space. Surrounding the thyroid parenchyma is a very thing layer of connective tissue, the glandular capsule, and between this and the surgical capsule is the intercapsular plane of cleavage or surgical space. Crotti states that the musculocapsular and the surgical spaces are the most important so far as the surgical technic is concerned. The surgical

space is the "good plane of cleavage" which must be looked for if the surgeon wishes to make an easy and brilliant thyroidectomy. The surgical capsule must have been opened and the surgical space found before attempting to dislocate the goiter. He warns that the posterio-internal region of the surgical space must be absolutely avoided unless one wishes to expose the patient to parathyroid disturbances or injury to the recurrent laryngeal nerves.

Having properly exposed the goiter by dissecting with the finger along the plane of cleavage, one should ligate the lateral veins in order that these vessels may not be torn away and retracted into the wound. Hemostats may then be applied to all visible vessels and the resection begun. The next important step is to free and isolate the superior pole by dividing the superior thyroid vessels between double clamps, and separating it from the larynx and trachea. Downward and forward traction is then made on the goiter while the resection is carried toward the isthmus. At this stage it is well to locate the large branch of the inferior thyroid artery which enters the gland near the middle of the lobe. Failure to secure this vessel may cause it to be torn and retracted and injury to the recurrent laryngeal nerve result in the attempt to catch the bleeding vessel. The vessels at the lower pole are treated in the same manner as those at the upper pole. An assistant holds the gland and keeps up continual traction toward the isthmus, in this way controlling hemorrhage. One should never apply hemostats too hurriedly. By traction or pressure, the field may be kept dry at all times. Occasionally it may be necessary to pack a cavity for a few moments.

In large adenomatous goiters or in bloody exophthalmic goiters where many clamps are required, it is advisable to stop the resection at this stage and to tie off the vessels, otherwise they may become twisted and torn off. The superior and inferior thyroid vessels should be double tied. The smaller superficial vessels may be tied off by hand. It is advisable to stick tie the

more inaccessible vessels using a mattress stitch.

Crile[2] believes it is important to avoid contact with the trachea and the larynx by a sharp, bloodless dissection above the line of cleavage, and hence at a sufficient distance from the trachea and larynx to tie the vessels, without including the sensory nerves of the trachea, leaving on the trachea an undisturbed biologic coat. He believes the brain interprets injury to these sensory nerves the same as a foreign body in the trachea, and that tracheitis will develop. This in turn may terminate in bronchitis and broncho-pneumonia.

If it is an exophthalmic goiter, resection is completed on the opposite side in a similar manner. In case of an adenoma, the opposite lobe should always be carefully examined for any evidence of pathological changes. Search should always be made in these cases for a substernal or intrathoracic projection.

It is most important that the field should be left dry. The patient should be made to cough and strain until every bleeder is ligated. It is impossible to secure complete hemostasis in many cases owing to a persistent slight oozing. It is advisable to pack these cases with one or several strips of a one inch plain sterile gauze. It is an excellent remedy for surgeon's insomnia. This gauze should be shortened a few inches on the third day, the amount depending upon the ease with which it can be withdrawn. Usually it can be entirely removed on the fourth day.

The most serious complication in thyroid surgery is injury to the recurrent laryngeal nerves. The easiest way to injure these nerves is to attempt a very rapid bloody dissection, applying clamps at random and in all directions. In suturing the gland one can easily throw a ligature around the nerve. Mayo has pointed out that clamps should be applied and sewing done in the direction of the nerve and not across it. One should at all times maintain a dry field and not apply clamps until he can clearly see what tissue he is encroaching upon.

Resection should be within the capsule.

If the operation proves more difficult than anticipated, if the gland is very vascular and friable and there is severe hemorrhage, or if the pulse becomes too rapid and weak, it is advisable to stop the operation at once. Ligate all vessels and pack the wound open. Blood transfusion may be indicated. The operation may be completed in twenty-four hours or if necessary postponed a week. It may be well to repeat that operation should be postponed altogether on some cases that show evidence of marked hyperthyroidism. Cases that may appear in excellent shape an hour before operation may "go all to pieces" when one is about to operate. Then it is well to do merely a hot water injection or a ligation, or if this has already been done, to postpone the operation.

The amount of gland tissue to be left depends somewhat upon the type of goiter. The amount to be left should in general be the functional equivalent of a normal gland. This would mean only a small portion of an exophthalmic gland; but in the case of a large colloid or non-toxic adenomatous goiter a bulk larger than a normal thyroid is required because the colloid and simple adenomatous goiter is not as active as the normal gland. It was very common to see recurrences after lobectomies, but one seldom sees this condition following a resection. Care should be taken not to leave any small adenomas or a pyramidal lobe.

After all bleeding is checked a small rubber tube is inserted in the midline and the muscles sutured. The skin may be closed by a subcuticular stitch, dermal, or clips. The clips are usually removed within forty-eight hours and the dermal on the fourth day, unless there is a gauze pack. The rubber tube is removed at the end of twenty-four or forty-eight hours. The gauze pack not only serves to check hemorrhage but it facilitates the drainage of toxic secretions.

In cases of marked hyperthyroidism, Crile is now leaving the wound wide open for from six to forty-eight hours. No attempt is made to suture the muscles and the wound is packed with 1-5000 flavine gauze. He believes the advantages of delayed closure are: It shortens the time of operation. It may cut off the last fatal minute. There is practically no postoperative pain or discomfort. It prevents the absorption of wound secretions. Wound secretions are believed to play an important part in postoperative hyperthyroidism. I saw Crile do a number of cases with this method with excellent results. He told me that since adopting this plan he has had no occasion to use the ice pack method of combating post-operative hyperthyroidism. The only disadvantage to this method is that there is a slight tendency after the first six hours to increased contamination.

The technic outlined above, unless otherwise indicated is that which I learned from C. H. Mayo and his associates.

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Postoperative Treatment of Goiter.

The secret of the successful postoperative treatment of toxic goiter is to anticipate and prevent if possible the development of complications. The following rules may be considered for the general routine treatment.

When the patient is brought down from the operating room he should be placed in a semi-erect position in a bed that has been previously warmed. C. H. Mayo has found this position to be the most satisfactory. Willard Bartlett, on the other hand, advocates placing the patient upon his face with the body slightly elevated and the head hanging down. He contends that the bifurcation of the trachea thus becomes the end of the tube which drains down hill as far as the lips, and in consequence during the first few hours the patient is completely freed of all early hypersecretion. Crile allows his patients to assume the position of greatest comfort.

To combat thirst and increased metabolism water is given in amounts up to 3000 cc. for twenty-four hours. Crile requires his cases to have a minimum of this amount. Since the work of Rowntree on water intoxication, W. J. Mayo has suggested that the intake of fluids be limited to 3000 cc. for twenty-four hours. Crile prefers to give the fluid subcutaneously by the Bartlett novocaine method, and does not use proctoclysis as he considers it less satisfactory and more objectionable to the patients. He considers intravenous injection of fluid contra-indicated and dangerous. Following ligation his cases are allowed to drink freely by mouth and are only given subcutaneous saline if the patient fails to take the minimum required amount or vomiting persists. At the Mayo Clinic proctoclysis is given routinely, and if vomiting persists fluid is given subcutaneously. As soon as the postoperative vomiting lessens, patients are given small amounts of water by mouth. If the vomiting continues, water by mouth is withheld. The advantage of local anesthesia is in the absence or great-

ly decreased postoperative vomiting.

The routine use of an ice bag to the heart is suggested in all toxic cases. In the very severe cases it is well to place one or more on the heart and to apply an ice cap to the head.

Some surgeons object to the routine use of morphine. It should be used discriminately but in sufficient amount to prevent the development of postoperative restlessness and hyperexcitability. It is usually a bad prognostic sign when the patient begins to pick at the bed clothes.

Bartlett advises the use of steam in the room for several hours after operation to facilitate the expectoration of the hypersecretions and to lessen the discomfort of sore throat.

Some surgeons remove the drainage tubes at the end of twenty-four hours, and others on the fourth day with apparently the same end results. In his most toxic cases Crile uses a secondary closure of the muscles and skin after six hours or more, and at this time he removes a flavine pack. In some cases he leaves in a gauze drain for twenty-four hours. Pemberton uses strips of plain gauze when there has been considerable hemorrhage, and in very toxic cases with the same idea of aiding drainage of toxic secretions and lessening the possibility of postoperative hemorrhage. Removal of these gauze drains is started on the third day, and they are taken out on the fourth or fifth day. It is better to delay a day than to be in too great a hurry and start a hemorrhage. Skin stitches are removed on the fourth day or on the day the gauze drain comes out.

Patients are given an enema on the third day and allowed to be up unless the pulse is above 120, or there has been some post-operative complication, as hyperthyroidism.

The wound should be dressed daily until the fourth day and every other day thereafter until drainage has ceased. Crile uses hot packs in about 60 per cent of his cases.

Postoperative Complications and their Treatment.

The following are some of the postoperative complications that may be encountered in surgery of the thyroid:

Hyperthyroidism.
Shock.
Hemorrhage.
Cardiac failure.
Paralysis of one or both recurrent laryngeal nerves.
Tetany.
Pulmonary complications.
Tracheal obstruction.
Air embolism.
Hematoma of the wound.
Wound infection.
Thyroiditis of the remaining portion of the gland with resultant myxedema.
Psychoses.
After treatment.

Hyperthyroidism.-- Perhaps the most common and dreaded complication of thyroid surgery is hyperthyroidism. Why does postoperative hyperthyroidism occur? A great many hypothetical theories have been advanced as to the meaning of this condition, but it is a fact that we know more about its prevention and treatment than we do of its etiology and significance. With the improved methods of clinical diagnosis, with the realization that exophthalmic goiter is never an emergency operation, with better surgical technic and team work, this complication is less frequent and less dreaded than it was a few years ago. Some men believe that this condition results from the absorption of toxic wound secretions; yet a marked reaction following ligation or even boiling water injections into the gland is not uncommon. Likewise fatal hyperthyroidism has resulted following tonsillectomy and operations elsewhere in the body. Kocher and Riedel believed that hyperthyroidism was due to general anesthesia, yet it may follow the use of local anesthesia. Crile has asserted that postoperative hyperthyroidism is due to shock. Others have maintained that this state is related to thymic hyperplasia. Crotti believes that he has observed this condition

less often since he has routinely combined thyroidectomy with thymectomy, but this idea is not supported by other observers.

Plummer has said that the evidence that high metabolism dominates the clinical syndrome of hyperthyroidism is generally recognized, but that he believes the rate of metabolism is dependent upon the thyroid hormone, and that this function is not specific for certain tissues, but is common to all the cells of the organism. Increase or decrease in the rate of the metabolism dependent upon this hormone to a sufficient degree gives rise to the clinical syndromes of hypothyroidism and hyperthyroidism.

Since hyperthyroidism is still a matter of theoretical conjecture, we must consider its clinical manifestations and their prevention. To all appearances postoperative hyperthyroidism is identical with that stage of Grave's disease which has been called a crisis, except that the symptoms are greatly intensified. There is palpitation, tachycardia, tremor, vomiting, fever, excessive sweating, insomnia, extreme irritability and nervousness, and in the more severe cases hallucinations, psychosis, and jaundice. There is marked dilatation of the heart and often renal impairment. In one case I observed a blood urea of 450 mg. per 100 cc. of blood. Exophthalmos is intensified; the patient is very restless and picks at the bed clothes; his extremities become chafed from constantly moving them about; as the fever rises, restlessness changes into delirium. Unless there is sufficient intake of fluids the tongue becomes dry and parched from the raging metabolism. The basal metabolic rate has been observed to pass the plus 100 per cent mark in some cases. The fever ranges from 101^{0} to 106^{0} or higher. The pulse rate is usually above 150.

This complication may be guarded against by careful selection, testing and preparing of cases by preliminary procedures such as intensified rest, hot water injection and ligations. Whether the gland is "stolen" after the manner of Crile, or thyroidectomy is performed after gaining the patient's confidence,

as is done at the Mayo Clinic, depends upon the surgeon and the individual case. Any operative procedure when the disease is on the upward trend or on the crest of a wave of hyperthyroidism may precipitate a crisis. Local anesthesia and gas oxygen alone or combined is the anesthesia of choice in the hands of many surgeons. Others prefer ether. A rapid yet bloodless operation minimizes the risk of postoperative hyperthyroidism. It is better to stop operating as soon as possible if the patient's condition does not justify going ahead.

Crile believes that since adopting his method of secondary closure of wounds and packing them wide open with gauze to facilitate the drainage of toxic secretions, he has not only shortened the time of operation with the resultant prevention of complications, but he has eliminated postoperative hyperthyroidism. Pemberton[11] believes that the use of gauze packing and drains as advocated by Crile an excellent procedure.

The use of ice bags, of fluids, and of narcotics is mentioned in the chapter on postoperative treatment.

If prevention has failed and hyperthyroidism has developed, the indications are to combat the increased metabolism with fluids, to reduce the fever with sponges and ice bags, to induce quiet and sleep. Needless to say the less narcotic required the better. Ice packs are somewhat dangerous but may be tried in desperate cases.

If the patient lives forty-eight hours a prognosis can usually be given, provided broncho-pneumonia does not develop as an additional complication.

Shock.-- With the marked advancement in surgery of the thyroid the past few years, shock is no longer a frequent complication. Treatment is largely based on prevention. There is no generally accepted theory regarding the etiology of this condition, but there are better formulated views regarding

its prevention and treatment. The following prevalent views concerning the etiological factor in shock have been discussed by Seelig:

1. Vasomotor exhaustion.

2. Cardiac spasm and eventual failure.

3. Inhibition of the functions of all the organs.

4. Deficiency of carbon dioxide in the blood.

5. Morphologic changes and eventual, partial or complete disintegration of the ganglion cells. It is impossible to review his discussion in this paper, but the reader is referred to this excellent abstract by Seelig as well as to the exhaustive work by Crile.

Prevention of shock in goiter surgery is based on the careful selection and preoperative preparation of cases. Dehydrated patients should be built up until their condition warrants surgical interference. Proper rest for the body as well as for the nervous system should be insured both before and during the operation. Preliminary blood transfusion may be indicated. Crile has emphasized the importance of maintaining body warmth on the operating table. A dry operating field points to a better prognosis. A rapid accurate resection is desirable, providing there can be gentle manipulation of the tissues. As previously mentioned local novocain and gas-oxygen alone or combined as indicated in the individual case, is the anesthesia of choice and minimizes the risk of shock.

If shock occurs, the generally accepted methods of treatment should be instituted without delay; elevate the foot of the bed; maintain body warmth by external heat; administer subcutaneous injection of saline; give shock enema. Opinion differs regarding the use of adrenalin, pituitrin and blood transfusion.

Hemorrhage.-- Postoperative hemorrhage may be guarded against by observing the following steps in the technic of thyroidectomy: Tie off those

vessels which have been ligated after resection of one half the gland before attempting to resect the other half of the gland; before beginning resection of the gland carefully ligate the lateral veins. These procedures prevent the vessels from tearing off and retracting. Stick ties insure better hemostasis. When the operative field is apparently dry the patient should be induced to cough or strain. This method will commonly disclose one or several bleeders that might otherwise have been overlooked. It is impossible to secure absolute hemostasis in some cases, and in these the wound should be packed with strips of gauze which will also act as drains for the toxic secretions.

Postoperative hemorrhage usually occurs the day of the operation and may be detected by signs of increasing dyspnea, choking spells, a rapid pulse that grows weaker, cyanosis, and a tense swelling in the neck. No time should be lost in opening the wound, expelling the clot, and ligating the vessel. It may be impossible to locate the bleeding vessel at first but the hemorrhage can be controlled by packs until conditions are more suitable for examination.

Pemberton[10] says that the frequency of secondary hemorrhage is due, first, to the fact that the remaining portion of the thyroid gland is movable and following the movements of the trachea a ligature may become loosened, and second, that veins are often broken during the dislocation of a lobe from its bed without the knowledge of the operator.

Cardiac failure. -- This condition is seldom seen uncomplicated. It usually occurs in connection with postoperative hyperthyroidism. In exophthalmic goiter death may result from acute cardiac dilatation. In toxic adenoma, cardiac death usually results from an acute cardiac strain superimposed on a heart that has been damaged for many years. Such a heart is usually found to show a marked chronic myocardial degeneration. Digitalis is the best safeguard against cardiac failure, but it must be given before operation.

Paralysis of the vocal cords. -- Crotti believes that injury to the inferior laryngeal nerve is most liable to occur:

1. When the inferior thyroid artery is ligated; hence the indication to perform the operation far from the thyroid, namely, on the inner border of the carotid sheath.

2. When resecting the gland; hence the indication to leave a thick layer of glandular tissue in connection with the posterior capsule. He believes that if these two requirements are observed there should be no direct injury to the inferior laryngeal nerve.

We may consider then that injury to the nerve during the operation either by section, ligation, stretching or pinching comes under the classification of direct causation. While under indirect causes are paralysis from nerve compression by scar tissue, and edema of the nerve or surrounding tissue.

Pre- and post-operative examination of the larynx should be made routinely in all cases of goiter for the protection of the surgeon as well as for the patient. If the preoperative examination shows paralysis of one cord, the surgeon must exercise the greatest care to avoid injury of the remaining sound cord. The prognosis in bilateral abductor cord paralysis is not only serious as to return of function but also as to life. As a rule the patient is required to wear a tracheotomy tube and is subject to frequent severe choking spells. Death from aspirative pneumonia may occur.

From a research standpoint this condition offers many interesting problems, and a great deal of excellent work has already been accomplished. Judd, New and Mann, after extensive animal experimentation, came to the following conclusions:

1. Section of the recurrent laryngeal nerve produces complete paralysis of the vocal cord of the corresponding side which in all

probability will be permanent.

2. Ligation of the recurrent laryngeal nerve with linen, chromic catgut or plain catgut produces complete and probably permanent paralysis of the vocal cord of the corresponding side.

3. Stretching the recurrent laryngeal nerves acutely in a manner similar but of longer duration and greater intensity than occurs in operation does not impair the function of the vocal cord. Stretching the nerves for a long period, as over muscles, impairs the function of the vocal cords, but the impairment is probably due to the operative trauma and not to the stretching.

4. Pinching the nerves with a hemostat in a manner similar to that which may occur in an operation produces temporary paralysis of the vocal cords. Restoration of function always occurs, the length of time necessary for restoration depending on the anatomical point at which the nerve was crushed. Thirty to sixty days is required for complete regeneration of the nerve.

5. Exploration of the nerves produces an effect on the vocal cords depending on the amount of trauma to which the nerves are subjected. Careful dissection will probably not produce any effect.

Using local anesthesia and talking with the patient during the operation enables the surgeon to detect immediately any injury to the cord. Pemberton[10] believes that injury to the nerve during the course of the operation may often be detected by the sudden change in breathing, such as rasping with inspiratory strides. Cutting the offending suture may be followed shortly by the return to normal.

The prognosis following injury to one of the inferior laryngeal nerves is good as a compensatory swinging over of the other vocal cord occurs. The slight hoarseness that so frequently occurs following operation, and which

is probably due to edema of the nerve, usually disappears in forty-eight hours. Cases of functional aphonia are of common occurrence. Steam inhalations and the surgeon's assurance seem to cure both these groups. The normal voice is often restored in those patients in whom there had been impairment of the vocal cord preoperatively from pressure of the goiter on the nerve.

The writer was so fortunate as to assist Dr. Pemberton in a series of 350 thyroidectomies in which no cases of vocal cord paralysis occurred. I believe this excellent record may be partially attributed to an accurate knowledge of the anatomy, especially that of the nerves and arteries (gained by post-mortem anatomical dissection), applying the hemostats so as to close in the vertical line of the neck and not across it; maintaining perfect hemostasis at all times and never applying a hemostat until the field of operation is dry and clearly visible (accomplished by traction on the gland or pressure of the index finger beneath it and raising it up); leaving plenty of gland tissue; avoiding unnecessary haste; avoiding deep suturing; ligating of all vessels on one side before beginning to resect the remaining half of the gland; using local anesthesia in 90 per cent of the cases and conversing with the patient.

Pulmonary complication. -- With the more general adoption of local anesthesia, with the recognition of the importance of preoperative "colds", and with improved methods of surgical technic and postoperative treatment, the incidence of aspiration pneumonia has been considerably reduced. As pointed out by Bartlett, it is more apt to occur where paralysis of a vocal cord leaves the entrance to the air passages less than usually well guarded. As a matter of prevention it is important not to allow the patient to aspirate the secretions that tend to accumulate in the larynx following thyroidectomy. He should be assisted in getting rid of the phlegm either by posture or, if the secretions are tenacious, with steam inhalations.

Pneumonia is more apt to develop when it becomes necessary to do a tracheotomy for collapse, or obstruction, or because of bilateral paralysis of the vocal cords.

Treatment is similar to that used for pneumonia developing after other operations. Some men prefer to maintain a fluid intake of 3000 cc. for twenty-four hours; to give pneumococcus antigen 1 cc. daily, subcutaneously for three days; and to digitalize the heart with tincture of digitalis 2 cc. quid by mouth for two days. Sunshine and fresh air, of course, are indicated, together with sufficient nourishment.

Tracheal obstruction.-- Tracheal obstruction or collapse either at the time of operation or several hours later is one of the most serious complications in goiter surgery. At the time of operation it is seen most commonly in substernal or intrathoracic goiters. It is due as a rule to compression or deformity of the trachea when attempting to manipulate the intrathoracic portion. It is important to remember, therefore, to free the smaller lobe from the trachea first, and to dispense with all hemostats when the vessels can be ligated. This allows the surgeon to control the patient's breathing and gives the latter more confidence so that he does not become frightened and choke when traction is made onthe trachea.

Pemberton[11] says that collapse of the trachea during the course of the operation is frequently due to pressure obstruction from the goiter or the weight of the forceps; it occurs most frequently during or immediately after the elevation of a large growth on one side, and is usually the result of an adenoma, possibly unsuspected, lying behind the trachea or below the sternum on the opposite side. The obstruction is relieved by elevation of the second growth.

Tracheal collapse occuring several hours after operation is due to a falling in of the tracheal rings which have become softened by years of

pressure from the goiter. The softened portions of the tracheal walls are supported by the goiter as long as it is not disturbed. When the goiter is removed the walls have no support and no elasticity and are sucked in with each inspiration. Once the diagnosis is determined a tracheotomy should be performed without delay and long tracheal insufflation catheters inserted since the ordinary tracheal intubation tubes are too short.

Crotti considers a better method is to pass at the time of operation one or two threads through the collapsing walls and to suture them to the muscular belt, with just enough tension to maintain the collapsing walls far apart, but not so far as to tear the suture through. The head should then be immobilized so as to get the cervical muscles at rest. The threads will hold just long enough to allow the trachea to become adherent in its new position to the neighboring tissues, and consequently prevent any further collapse.

Considerable dyspnea results from cord paralysis and requires a tracheotomy if both cords are injured. Pemberton[11] believes that the dyspnea of patients with profound hyperthyroidism may be confused with the obstructive dyspnea and emphasizes the importance of opening the trachea in all cases if any doubt exists, for thus a life will occasionally be saved. He states that in performing a tracheotomy in a thyroidectomized patient, the mediastinal space should always be well walled off by a pack before the trachea is opened, to prevent a possible fatal mediastinitis.

Postoperative tetany.-- This complication was more frequent when lobectomies were being performed and is seldom seen today. The condition may follow the complete removal of all or of the greater part of the parathyroid tissue or an injury of the parathyroids or their blood supply.

Symptoms usually develop within the first forty-eight hours after operation. Boothby has called attention to the prodromal symptoms such as

headache and general weakness, accompanied by radiating pains down the extremities and chronic twitchings that may occur. Usually the onset is characterized by a pricking sensation and a slight stiffness of the fingers. The symptoms are almost constantly symmetrical and bilateral. As a rule they reach their maximum intensity on the third day. The upper extremities are most commonly affected and present the characteristic contraction spoken of as the "accoucher's" hand, which consists of flexion of the fingers at the metacarpal phalangeal joint with adduction of the thumb. Intercurrent contractures of the muscles of the face or trunk less often occur. Erb (1874) pointed out that in tetany the electric excitability of the motor nerves is increased; Trousseau (1851) showed that during intervals between spasms attacks could be brought on by compression of the main nerve trunk; Chvostek (1907) found that the facial muscles can be made to twitch by tapping along the course of the facial nerve; Weiss showed that a sudden contraction of the muscles frontalis corrugator supercilii and obercularis oculi occurs when the temporal and zygomatic branches of the facial nerve are percussed at the outer angle of the orbits. Crile called my attention to two diagnostic points of which I have seen no mention in the literature, namely, a circumoral pallor and a peculiar shiny glazed appearance of the forehead. Plummer believes that hysteria is an important factor in some of the cases.

Cases have been reported in which death occurred within three days after operation, but today tetany seldom persists for more than forty-eight hours. I have seen a few cases, however, in which the symptoms persisted in a mild form for a period of several months. As in humans so also in animals we may observe a great variety in the form and intensity of tetany. Crotti states that dogs develop a markedly acute and rapidly fatal tetany after complete thyroidectomy, while monkeys show a more chronic form of the disease. He also points out that postoperative tetany, no matter whether severe or light, must

always be considered as a serious complication, since we know that even the slightest form of tetany will, for no apparent reason, suddenly show marked exacerbations which may terminate in death. Crotti believes that postoperative tetany may retrocede spontaneously in about 35 per cent of the cases, but if death intercedes, it is caused by spasm of the glottis, of the diaphragm, or of the bronchi.

The treatment of postoperative tetany with parathyroid extract or by parathyroid transplantation alone has not proved satisfactory, whereas excellent results have been obtained by the administration of calcium lactate. It may be given by mouth or rectum in a 10 per cent solution, 4 gm. every three hours, or subcutaneously in a 5 per cent solution. It may also be administered intravenously. If the patient still possesses some parathyroid tissue, calcium lactate may tide him over the danger point until compensatory hypertrophy of the parathyroid tissue can occur.

Crile advocates 20 cc. of a 25 per cent solution of magnesium sulphate for very severe contractures. For the routine treatment of these cases he gives parathyroid 1/10 to 1/5 gr. three times daily, thyroid extract, 2 gr. daily, and calcium lactate 15-20 gr. four times daily. This treatment is modified in the milder cases.

Embolism.— Although not commonly seen, air embolism is probably the most serious of all complications that may develop in goiter surgery. It may occur after a ligation as well as a thyroidectomy. It is more likely to develop in the removal of intrathoracic goiters, because then the veins may be torn accidentally and the opening not discovered. Air is then aspirated into the thyroid veins and passes thence into the internal jugular and innominate veins and thence to the right auricle. The veins may be adherent in malignant goiters; thus they are unable to collapse and prevent the aspiration of air.

While the clinical signs and symptoms of embolism may develop on the operating table, they more often occur several hours later and frequently not until the patient gets up. In the cases which I have seen, sudden fainting spells were followed by mild dyspnea. The patients became very pale, and developed cyanosis of the lips and extremities together with a failure of the circulation. In some cases there was no perceptible change in the pulse, in others the pulse became rapid and weak. In those cases in which the blood pressure was taken the systolic pressure dropped below 90 mm.

If death does not occur immediately, the patient should be given morphine and kept absolutely quiet. Since this condition is often induced by straining at stool, care should be taken to keep the bowels at rest for several days. The patient may survive the initial attack and succumb to a second one. Several of the cases which I have seen, in which a clinical diagnosis of embolism was made, recovered. Emboli may lodge in the lungs and cause infarction, and pleurisy or pneumonia follows.

As a prophylactic measure it is important to ligate all veins as one operates rather than to work with too great haste and tear the vessels while attempting to remove the gland.

Hematoma of the wound. -- Postoperative hematoma is not important but is rather an unpleasant complication which may usually be prevented. The best means of preventing hematoma is to secure perfect hemostasis. This is accomplished by requesting the patient to cough or strain before finishing the operation and ligating any "bleeders" that appear. Packing with plain gauze will help when it is impossible to obtain a perfectly dry field. A rubber tube drain is used routinely. The patient should be told not to allow his chin to rest on his chest continuously but to hold it erect at least part of the time. A rather firm dressing will aid him in this. If the hematoma develops, hot dressing should be applied three times a day and care taken to keep the

drainage tract open.

Wound infection. -- This is not a serious complication but it may be very annoying to the patient, especially if she is a young girl and a disfiguring scar results. Altho the infection in itself is not serious, it may induce other complications. Postoperative myxedema is probably the most serious and frequent complication of wound infection.

Thyroiditis of the remaining portion of the gland with resultant myxedema. -- Formerly it was considered that postoperative myxedema resulted from removing too much of the gland at the time of operation. Now we know that in the majority, if not all, of these cases myxedema develops because of a thyroiditis which destroys the remainder of the gland. For this reason it is important to observe all cases in which there has been wound infection for a considerable period of time in case myxedema should develop. While this condition cannot be prevented it can be properly treated and the patient kept in a normal state as long as he takes thyroxin. The work of Plummer and Kendall has simplified the treatment of myxedema so that by the use of the metabolic rate and thyroxin this condition can be treated scientifically and accurately. Briefly, Plummer treats his cases by first obtaining a series of metabolic rates to serve as a check, then injecting in two doses fifteen milligrams of thyroxin intravenously to bring the patient's metabolism to normal. By frequent readings of the metabolic rate under varying daily doses of thyroxin by mouth one can determine the exact dosage required to obtain the normal metabolism.

Psychoses. -- The incidence of postoperative psychoses is rather higher in thyroid surgery than in operative work in other regions of the body, due to the peculiar mental state of the toxic cases. The belief is held by some men that individuals who develop exophthalmic goiter are mentally predisposed to this condition. It is true that these individuals are often high-strung, rather nervous persons, who are under high tension. Certain it is

that mental derangement of almost every degree and type has been seen in these cases both before and after operation. It is seen more often in adults, and more frequently in the female than in the male. While confusion, hallucinations, fears, stupor, delusions and melancholia are frequent, the hysterical excitement type is probably the commonest form.

Da Costa believes there is a predisposition, either hereditary or acquired, in all cases of postoperative insanity, which the operation merely serves to stimulate and bring to a climax. He states definitely that a normal, healthy individual will probably never go insane following any surgical procedure unless it involves the brain, removal of the testicles or the ovaries. Barker says that the frequency of neurasthenic states, of anxiety states, and of phobic and obeisonal states in patients suffering from this disease is notorious. He says that outspoken psychoses (maniacal, paranoid and melancholic) are by no means uncommon in exophthalmic goiter.

Two very important factors concerned with these mental states are fear and worry, according to McKittrick. He believes that if one could fathom the innermost workings of the minds of patients coming to operation one would be astonished at the damage which fear alone has wrought. Crile and his co-workers have found that the brain cells suffer degenerative changes, the nucleus, nucleolus and cell body breaking down, a mere mass of protoplasm remaining, when they are subjected to overwork, infections, drug poisons, shock, fear or anxiety.

McKittrick states that in high-strung, nervous individuals, and most patients become nervous in view of an impending operation, the surgeon must maintain a constant attitude of optimism and encouragement; he must never lose sight of the fact that the patient is to be inspired with confidence. Once the condition develops, he advocates thorough eliminative measures and the giving of large amounts of water and alkalis by mouth, in the rectum, and under the

skin. Food should be given regularly with sufficient alkalis to keep down an acid intoxication. He says that bromides are very depressing and should be avoided, but that opium and hyoscine particularly should be employed. General hygienic measures are important.

General rules for postoperative after-treatment.--

Ochsner states that by far the most important point in the surgical consideration of this condition consists in the after-treatment. With careful after-treatment the majority of these patients may become as useful as they were before exophthalmic goiter developed. Failure in this consideration results in these patients developing a condition as bad, if not worse, than that with which they presented themselves primarily for surgical treatment. He adds that the surgeon should bear in mind that practically all of these patients belong to a class of neurotics, and that this undoubtedly had much to do with the development of their goiters primarily, and that in their weakened physical condition they will not be able to bear the wear and tear to which neurotic tendencies would surely expose a patient.

It is impossible to lay down one definite set of rules to be followed by all patients, since it is obvious that the poor man's wife cannot afford to have her breakfast served in bed as can one of the four hundred.

1. Patients should be told to retire early, sleep as late as possible, and to rest as long as possible, and to rest as long as possible after luncheon.

2. They should avoid excitement such as social functions, certain moving pictures, club work, politics, church work, etc.

3. Over-exertion from housework, office work, walking, driving, etc., should be forbidden.

4. Stimulating drinks such as tea and coffee, as well as tobacco should be avoided.

5. The importance of avoiding certain foods has been probably exaggerated. Patients should be encouraged to eat three good meals a day and more if their gastro-intestinal system is not upset. Neurasthenia, starvation, constipation, worry and thin people go together. Wit and humor, stout and happy people are usually associated.

6. The best advice I remember Plummer giving his patients was to turn out to pasture for three months and lead a life in the open. It is the hothouse plant and not the lumberjack that is neurotic.

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Postoperative Results of Goiter Surgery.

In 1920 I assisted Dr. Judd in reviewing the postoperative results of two hundred operations for goiter at the Mayo Clinic. Two series were studied, the exophthalmic group, and the cases of adenoma with hyperthyroidism. I will quote from one of his papers as follows:

"We have recently reviewed, as accurately as possible, the results obtained in 100 consecutive cases of hyperthyroidism in which operation was done in the year 1914....The mortality in the cases in which a thyroidectomy was performed was 2 per cent. Of this group of 100 consecutive patients operated on in 1914, we have been able to trace more than 90 per cent. Of these 66 per cent are free from all signs of the disease at least six years after operation... Apparently the last symptom to disappear is the exophthalmos, which is present in about 70 per cent of the cases before treatment. Slight nervousness persists for some time after most other symptoms have disappeared. In addition to the 66 per cent of patients who were cured, 13.5 per cent reported that they were considerably improved, and 5.5 per cent that they were slightly improved. Eleven of the 100 patients died after leaving the clinic. Most of them were much better for some time, and were apparently cured of their hyperthyroidism. Several, however, died in relapsing attacks."

The average preoperative basal metabolic rate was plus 32.7 per cent and the average postoperative rate was plus 9.2 per cent. The detailed study of the cases follows.

The year 1914 was chosen for the exophthalmic group because it was felt that a six year period in these cases should allow sufficient time to elapse for classifying the operative results as a success or failure.

The thyrotoxic group was chosen from the years 1917 and 1918 because it was at this time that a metabolic study of all the thyrotoxic cases

was begun. The average time elapsed since operation in these cases was two years.

The cases were first studied on a basis of the clinical histories and pathological findings and only those selected in which these agreed. There was a definite hypertrophy in all of the thyroids removed which were diagnosed by the clinician as exophthalmic goiter and by the pathologist as hyperplastic thyroid. The cases of thyrotoxic goiter all showed the pathological findings characteristic of that disease.

One hundred and fifty letters of inquiry were sent out to patients in each group and of this number replies were received from 110 patients in the thyrotoxic group and from eighty-eight of the cases of exophthalmic goiter.

Eighty-eight of the cases of thyrotoxic goiter were females whose average age was 48.8 years. In the same group there were twelve males averaging 48.4 years of age.

In the exophthalmic group there were eighty-three females, averaging 34.3 years and seventeen males averaging 36.6 years of age.

As has been pointed out by Plummer, thyrotoxic goiter usually commences early in life, but it is not until the goiter has existed for an average of almost sixteen years that the symptoms of hyperthyroidism develop to such an extent as to cause the patient to consult a surgeon. In the thyrotoxic group, goiter was first noticed at an average age of 29.8 years, in comparison with 31.3 years for exophthalmic cases, but the former group gave a history of goiter for 19 years 4.8 months, in contrast with three years and eight months for the latter. Likewise the cases of exophthalmic goiter gave a history of symptoms for only one year, nine months as compared with two years 5.8 months for the cases of Plummer's disease.

A study of the clinical histories with a view of ascertaining which symptoms were noticed previous to operation, which ones disappeared following operation, and which ones persisted, revealed some interesting figures.

The following are the most important symptoms noted by the clinician and patient before operation and by the patient postoperatively.

	Exophthalmic Goiters		Thyrotoxic Goiters	
	Preoperative	Postoperative	Preoperative	Postoperative
Nervousness	98	39	88	45
Tremor	93	21	83	6
Dyspnea	84	29	76	28
Palpitation	89	26	80	29
Tachycardia	79	24	72	23
Strength loss	89	13	79	17
Weight loss	89		92	
Vomiting	34		8	
Prominence eyes	70	25	6	
Change in voice	25	12	6	11
Heart mod. enlgd.	38		14	
Heart mkd. enlgd.	19		9	
Murmurs	33		28	
Edema	20		34	
Exophthalmos	67	25	3	
Thrill	48		4	
Bruit	72		10	
Avg.Normal Wt.	137.3#	Gain. 61 Av. 27.3#	151.1#	Gain. 82 Av.31.6#
Avg.Wt. at oper.	121.8#	Lost. 5 Av. 10.5#	131.7#	Lost. 3 Av.11.5#
Avg. pulse rate	122.6		111.	
Avg. S.B.P.	145.2		157.2	
Avg. D.B.P.	75.6		82.4	

It is interesting to note that the most predominant symptom persisting in each group is nervousness and that palpitation and dyspnea closely follow, and that 143 of the 175 cases show an average weight gain of thirty pounds.

In a great majority of the cases clinical examination revealed an enlargement of both right and left lobes of the thyroid. This is shown by the following table:

Enlargement of gland.

Exophthalmic Goiters		Thyrotoxic Goiters	
Rt. & lt. lobes	79 cases	Rt. & lt. lobes	49 cases
Rt. isth. & lt.	11 "	Rt. isth & lt.	14 "
Rt. lobe	4 "	Rt. lobe	17 "
Lt. lobe	3 "	Lt. lobe	10 "
Isthmus	1 case	Isthmus	5 "
Not stated in	2 cases	Rt. & isth.	4 "
		Lt. & isth.	1 case

Table of operations.

	Exophthalmic Goiters	Thyrotoxic Goiters
One preliminary ligation	30 cases	3 cases
Two preliminary ligations	34 cases	0 "
Primary thyroidectomy	36 "	97 "
Thyroidectomies:		
One lobe	4 "	9 "
One lobe & isth.	20 "	20 "
One lobe, isth.& pt.other	64 "	51 "
Part of each lobe	12 "	20 "

Results of operation. -- The following questions were asked the patients in the letters of inquiry:

1. Do you consider yourself cured as a result of operation ?

2. Do you consider yourself improved ?

3. Do you consider your condition unchanged ?

4. Do you consider yourself worse ?

Besides these questions the patients were given a list of symptoms, such as palpitation, rapid heart, prominence of eyes, etc., as tabulated above, to report on. Various factors which might have influenced these replies were considered. For instance if a patient reported himself as cured, but if his pulse record and symptomatic condition indicated otherwise, he was placed in one of the other groups. Likewise if a patient gave a negative symptomatic history and rather clearly attributed his condition to other influences, such as influenza, he was placed in group 1.

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The operative results are interesting in comparison with a group of 121 cases of results of operation for exophthalmic goiter at the Mayo Clinic for 1909 as presented by Dr. J. de J. Pemberton and Dr. Judd in 1915. In that group there were fifty-five (45.4 per cent) patients cured covering a period of six years. In the exophthalmic group discussed in this paper there were fifty-one (57.9 per cent) patients cured.

Following is a comparison of the operative results in the two groups of cases of exophthalmic goiters.

	1909		1914	
Cured	55 cases	45.4%	51 cases	57.9%
Practically cured	22 "	18.1%	7 "	7.9%
Marked improvement	7 "	5.7%	12 "	13.6%
Slight improvement	5 "	4.1%	5 "	5.6%
Condition not improved	8 "	6.6%	0 "	0
Hospital mortality	7 "	5.7%	2 "	2.2%
Died from all causes 14) Recurred 9, Insuff. data)	17 "	14.4%	11 "	12.8%

Discussion of significance of improved operative results.--

While the operative mortality was higher in the thyrotoxic group of cases, the results of operation were even more satisfactory than in the exophthalmic group. It may be said that approximately 66 per cent of the cases of exophthalmic goiter were cured, but practically 83 per cent of the cases of Plummer's Disease are well or practically cured.

The operative mortality in the cases of thyrotoxic goiter was much higher because the disease had extended over a great deal longer period of time and had left the patient in such a condition that operation was offered only as a last resort in an otherwise hopeless disease.

Table of thyrotoxic operative results.

Cured	63 cases	or	63 %
Practically cured	20 "	"	20 %
Marked improvement	5 "	"	5 %
Slight improvement	1 case	"	1 %
Not benefited	2 cases	"	2 %
Died	9 "	"	9 %
Six cases in hospital			6 %

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Conclusions:-- With an operative cure of 66 per cent in the cases of exophthalmic goiter and of 83 per cent in the thyrotoxic group, surgery would seem to be the ideal method of treatment for goiter.

The postoperative reduction in the metabolic rate is in proportion to the clinical improvement.

The most persistent postoperative symptom in both exophthalmic and thyrotoxic goiter is nervousness. Palpitation and dyspnea closely follow. Exophthalmos is the last symptom to disappear.

Cures resulting from operation in recent years have increased as surgical technic has improved.

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Mortality Factors in Surgery of the Thyroid

The technic of goiter surgery has been highly perfected by the work of Kocher, Mayo, Crile, Halsted, and others. These men have been largely responsible for:

(1) marked advancement in the early recognition and clinical diagnosis of toxic goiters,

(2) the fact that the majority of these cases come to operation much earlier today than they did ten years ago,

(3) the careful selection and preoperative treatment of these cases,

(4) the preliminary safety procedures, injections, ligations, etc.,

(5) the advancement in surgical technic and team work,

(6) improvement in the methods and modes of anesthesia.

In spite of this advancement the mortality rate still ranges from 0.5 per cent to 4 per cent because there are two important factors not perfectly understood, namely, the proper time to operate, and the treatment of postoperative complications. Probably inability to decide upon the proper time for operation is responsible for a higher mortality than is the operation itself. Crile and his associates maintain that operation should not be delayed, once the patient has been digitalized and the function of the kidneys ascertained to be satisfactory. Plummer, Mayo, and probably the majority of surgeons believe that this should not be looked upon as an emergency operation. They believe that the patient should be carried along for days and even weeks, with careful preliminary treatment until what they consider the ideal time for operation has been reached. Crile asserts that during this interval the disease is progressing and doing vital damage to all the organs.

Neither method yields perfect results. Statistics show that the number of deaths is about the same. To duplicate Crile's statistics would

indeed be difficult for the average surgeon. His results, however, represent the work of years of experience with a large amount of material. Not only has he perfected to a high degree his own surgical technic, but he has also developed to a high state of perfection the team work of all who assist him. In his own hands anoci-anesthesia has enjoyed remarkable success. These advantages the average surgeon cannot hope to possess.

The average surgeon could not do a ligation or a thyroidectomy on all cases of toxic goiter that had been under his observation for less than one week. His mortality rate would increase alarmingly. I have often observed a case in crisis for two weeks at a time having vomiting spells and diarrhea day and night, with a pulse of 150 and over, a temperature of 104° or higher, with heart markedly dilated and decompensated, unable to sleep, and extremely agitated by the slightest noise or disturbance in the room. Surgery certainly would be attempted at a great risk in these cases. I have seen death follow so simple a procedure as a hot-water injection or a ligation. The condition of these patients was far better than the state of a patient in a crisis.

It is interesting to trace over the past thirty years the marked reduction in mortality of operations on the thyroid. In 1909 C.H. Mayo[2] said, "In our early surgical work in hyperthyroidism, beginning some fifteen years ago (1894), only the most desperate cases were thus treated, and we considered results up to the average which gave 25 per cent mortality in the first sixteen cases. One of these fatalities occurred on the table. Better judgment in selecting a favorable moment for operation, with more careful preliminary preparation of the patient, and there were but three deaths in the next forty operations for the disease...

"In our next series there were in all 574 cases of simple, colloid, or diffuse adenomata.... Two operations were incisions and drainage of acute inflammatory conditions. There were four deaths in this series, one

being from lobar pneumonia on the eighth day, another from two severe delayed hemorrhages, one from shock in which we found brown atrophy of the heart, fatty infiltration of the liver with gall-stones, and one from septic pneumonia....

"There were 405 cases of marked hyperthyroidism operated upon with nineteen deaths.... In the most aggravated cases where there was dilated heart, adenoma and ascites, preliminary preparations were frequently prolonged for several weeks before the operation could be undertaken....

"There were 295 cases of removal of more or less of the gland, with eighteen deaths, seven of which occurred in the first forty-six operations.... After all has been said concerning the various dangers from operating for ordinary adenomatous goiter, we consider hemorrhage, either primary or delayed, with the efforts made to control this usually accidental condition, as the prime cause of death. Delayed hemorrhage usually occurs from including some muscle fiber in the ligation of the superior thyroid artery."

In 1914 C. H. Mayo[3] stated, "The great lowering of mortality following operation for exophthalmic goiter is due less to trivial details of technic than to the better judgment in the preparation of patients, the selection of a time, type, and extent of operation, and its division into stages with varying intervals of rest. The high mortality of the past is no longer a determining factor against the surgical treatment. As many as 278 consecutive operations have been made on the thyroid between deaths occurring from the operation. The average operative mortality at present probably varies from 1 to 3 per cent."

In 1920 C. H. Mayo[4] said, "The mortality rate has been greatly reduced during the last twenty years. The old vicious circle of late operation and high mortality and the high mortality conducing to a late operation has been largely overcome. More and more patients with hyperthyroidism are seen early, and the natural risks are thereby greatly reduced. Now only about 20 per cent of these patients come in the late stages. The consequent reduction

in mortality is not wholly due to the surgeon's increased ability and technic, but partially to the general advance of professional knowledge and to the diagnostician's cooperation. We were greatly pleased in an early series to perform forty-six consecutive operations for exophthalmic goiter between deaths; in a later series seventy-two, and still later 144 between deaths. According to the condition of the patients and best judgment in their treatment, the mortality will vary from 0 to 3 or even 4 per cent in various groups of 100.

Crile says, "The 'bad risk' patient should be protected against-- (1) suboxidation, (2) inhalation anesthesia, (3) want of water, (4) pain, (5) absorption of wound secretions, (6) infection, (7) fear and worry, (8) postoperative hyperthyroidism, (9) postoperative hypothyroidism.... By the application of these measures, the mortality rate of all thyroidectomies has been reduced to 1.3 per cent; of thyroidectomies for exophthalmic goiter, to 1.8 per cent; of ligations, to 0.6 per cent. Our final series, still unbroken, includes 322 thyroidectomies and 139 ligations without a death."

Pemberton reports that in a series of 542 operations for the removal of substernal and intrathoracic goiter at the Mayo Clinic there were sixteen deaths, a mortality of 2.9 per cent. Eleven (68 per cent) of those died from acute hyperthyroidism seventy-two hours following operation.

A study of the mortality records for goiter operations at the Mayo Clinic during the years 1918-19-20 reveals several interesting complications. A review of fifteen cases shows the following possible causes and factors relating to death:

1. Exophthalmic goiter. F. 42 yrs. 5 months history. Weight loss 36 lbs. B.M.R. plus 70 per cent on admission. B.M.R. plus 58 per cent following first ligation. Death followed second ligation and was due to acute hyperthyroidism and cardiac failure.

2. Exophthalmic goiter. F. 49 yrs. 8 months history. Weight loss 26 lbs. B.M.R. plus 49 per cent on admission. Following double ligation of superior thyroid arteries patient went home for 3 months. Returned in worse condition. B.M.R. plus 68 per cent. Quadriceps loss 4. Rest and medical treatment for 1 month. Operation very difficult because gland was friable, brittle and vascular. Not digitalized. Cardiac failure.

3. Exophthalmic goiter. F. 41. History of 18 months. Weight loss 18 lbs. B.M.R. plus 30 per cent. Developed psychoses 6 days following operation. Died 9 days after operation. Manic depressive.

4. Exophthalmic goiter. M. 11 yrs. History of 2 years. Weight loss 10 lbs. Strength loss plus 3 per cent. B.P. 154/64. B.M.R. plus 51 per cent. No reaction to quinine-urea injection. Died day after ligation. Belonged to peculiar juvenile type of long boned children. Chronicity and large persistent thymus, factors. Hyperthyroidism. Cardiac failure.

5. Exophthalmic goiter. F. 35 yrs. History of 1 year. Weight loss 13 lbs. Strength loss 3. B.P. 170/80. B.M.R. plus 85 per cent on entrance. Had double ligation and 3 months rest at home. Failed to gain weight. B.M.R. dropped to plus 64 per cent. Day following thyroidectomy developed dyspnea and edema of glottis. Tracheotomy done. Autopsy revealed edema of larynx and tracheal stricture. Not digitalized.

6. Exophthalmic goiter. F. 46 yrs. History of 2 years. No weight or strength loss. Condition good. Day following thyroidectomy had two attacks of cyanosis with tonic and clonic contractures. Emboli suggested. Empyema developed. Pulmonary embolism followed by empyema clinical cause of death.

7. Simple adenoma. F. 22 years. Non-toxic. Goiter for 10 yrs. Following operation developed crowing respiration. No evidence of hemorrhage. Death due to tracheal collapse. Probably recurrent laryngeal nerve paralysis.

Autopsy not obtained.

8. Exophthalmic goiter. F. 37 yrs. History of 11 yrs. Weight loss 66 lbs. Edema legs 2. B.P. 165/70. B.M.R. on entrance plus 97 per cent. Following two ligations and 3 mos. rest at home B.M.R. dropped to plus 65 per cent. Was under treatment for diabetes. Sugar free at time of operation but considered risk 3 with a mortality risk of 10 per cent. Operation difficult. Gland very friable. Acute hyperthyroidism. Bilateral pseudo-lobar pneumonia. Not digitalized.

9. Multiple adenoma with hyperthyroidism. F. 63 yrs. History of 3 yrs. B.M.R. plus 60 per cent. Weight 85 lbs. Mitral degeneration. Risk 3. Following partial thyroidectomy developed acute purulent pericarditis. Autopsy revealed same plus myocarditis. Digitalized.

10. Multiple adenoma without hyperthyroidism. F. 36 yrs. History of 2 yrs. No weight or strength loss. Good condition. Died suddenly 18 hrs. after thyroidectomy. No evidence of hemorrhage. Clinical diagnosis embolism. Not digitalized.

11. Exophthalmic goiter. F. 40 yrs. History of 10 yrs. 17 lbs. weight loss. B.M.R. plus 29 per cent. Developed tracheal collapse. Tracheotomy done. Died of broncho-pneumonia. Digitalized.

12. Exophthalmic goiter. M. 43 yrs. History of 5 mos. Weight loss 39 lbs. B.M.R. plus 67 per cent. Died two days after ligation. Clinical diagnosis paralytic ileus.

13. Multiple adenoma without hyperthyroidism. F. 40 yrs. Goiter for 17 yrs. Following thyroidectomy developed bilateral hydrothorax - bilateral broncho-pneumonia, and acute nephritis. Clinical diagnosis confirmed by autopsy.

14. Multiple adenoma without hyperthyroidism. F. 40 yrs. Goiter for 15 yrs. B.P. 170/82. While taking a drink of water on the day following

thyroidectomy patient fell back dead. Clinical diagnosis pulmonary embolism.

15. Multiple adenoma without hyperthyroidism. F. 41 yrs. Goiter for 25 yrs. B.P. 198/95. Developed acute urinary retention following thyroidectomy. Uremic convulsions and death occurred on fifth day.

It is apparent from the brief summary of these cases the many different complications that may develop in surgery of the thyroid, regarding which the surgeon has little or no control. Nevertheless, when one considers the thousands of successful operations performed for goiter and the high percentage of cures, the risk is indeed small, and the results are highly gratifying. While the surgeon is powerless to prevent most of the complications just reviewed, he must exercise great care and deliberation in choosing the proper type and time of the operation. It should be his aim to prevent, if possible, the development of postoperative hyperthyroidism, postoperative hemorrhage, and postoperative pneumonia.

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1. Crile, G. W.:

2. Mayo, C. H.: A consideration of the mortality in one thousand operations for goiter. Surg., Gynec. and Obst. 1909, viii, 237-240.

3. Mayo, C. H.: Hyperthyroidism: Primary and late results of operation. Surg., Gynec. and Obst. 1914, xix, 351-359.

4. Mayo, C. H.: The thyroid and its diseases. Surg., Gynec. and Obst. 1921, xxxii, 209-213.

5. Pemberton, J. de J.: Surgery of substernal and intrathoracic goiters. Arch. Surg. 1921, ii, 1-20.

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Fig. 1 - A case of multiple nontoxic adenomata of the thyroid.

Fig. 2 - Gross specimen of a nontoxic adenoma of the thyroid.

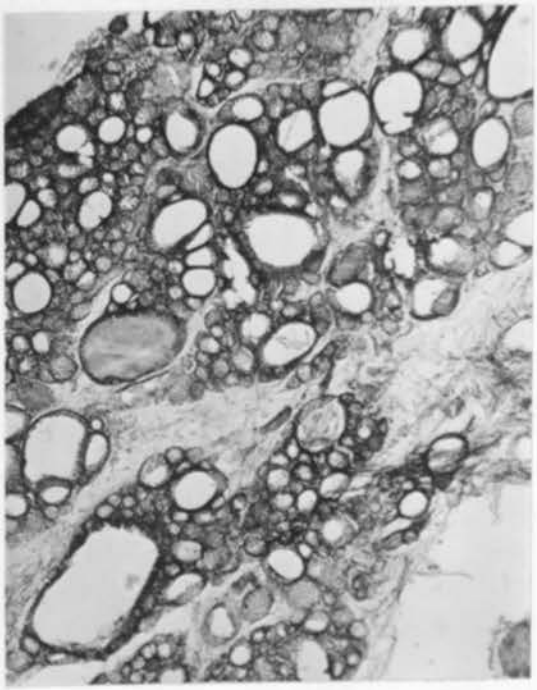

Fig. 3 - Microscopic view of the same (Fig. 2) nontoxic adenoma.

Fig. 4 - Simple adenoma of the thyroid.

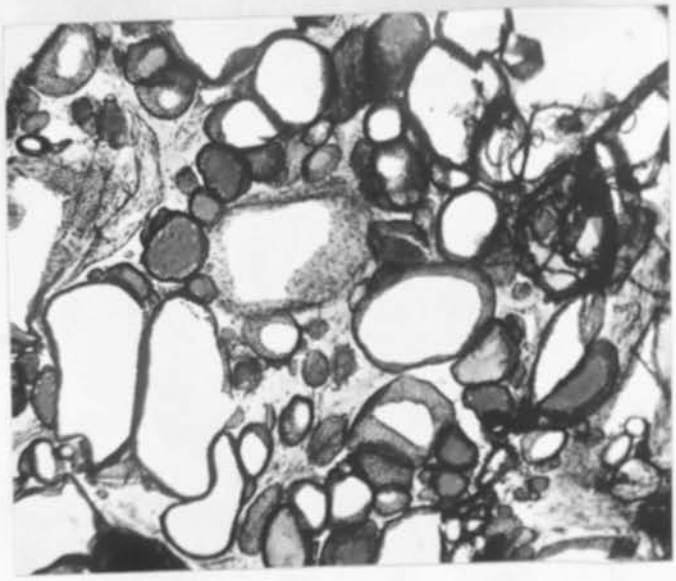

Fig. 5 - Microscopic view of simple adenoma of the thyroid (Fig. 4).

Fig. 6 - Gross appearance of a simple adenoma of the thyroid.

Fig. 7 - A case of exophthalmic goiter. There is only a slight diffuse enlargement of the gland. The patient shows no exophthalmos yet the basal metabolic rate may be very high in cases such as this.

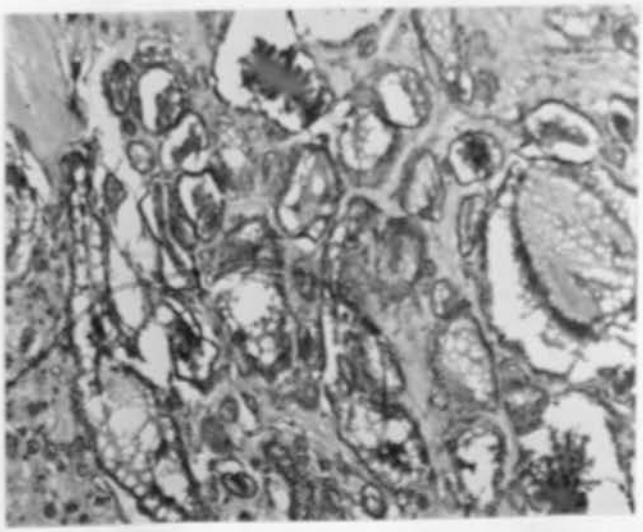

Fig. 8 - The same case (Fig. 7) showing the microscopic appearance.

Fig. 9 - The exophthalmic goiter on gross appearance has a typical beefy, meaty color and look.

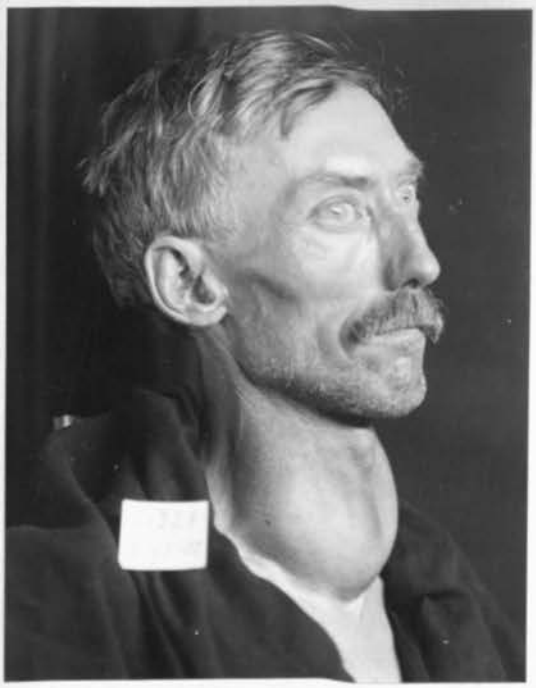

Fig. 10 - A case of exophthalmic goiter. There is a marked symmetrical enlargement of the gland. The patient shows moderate exophthalmos and loss in weight.

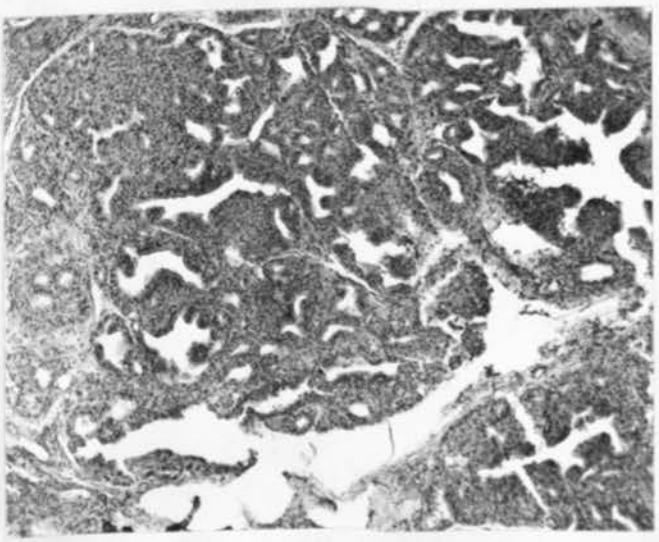

Fig. 11 - The same case showing the microscopic view.

Fig. 12 -Exophthalmic goiter. Gross appearance of the thyroid.

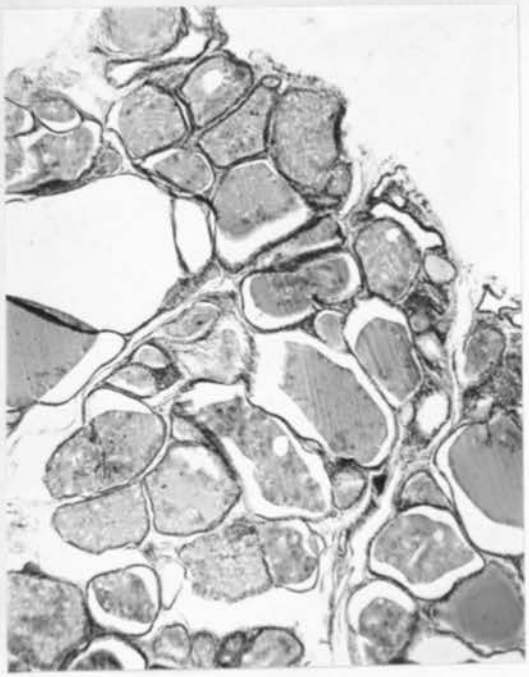

Fig. 13 - The thyroid gland in the resting stage. The alveoli are distended with colloid.

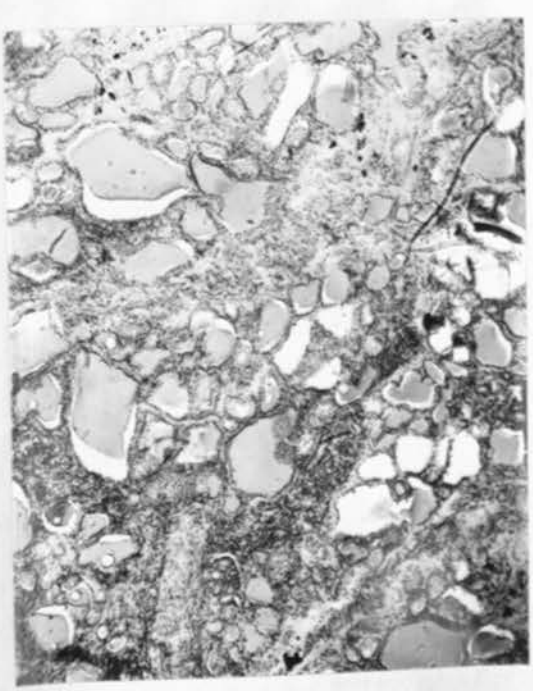

Fig. 14 - Colloid thyroid. Showing mild activity of the gland and the beginning development of the small adenomata.

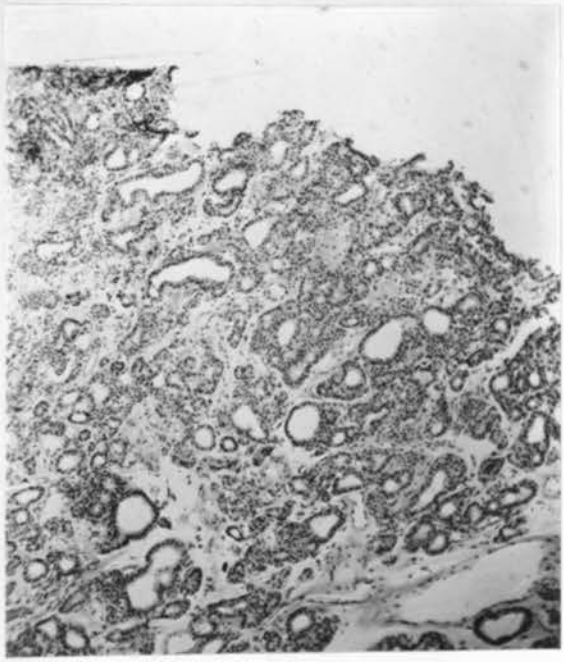

Fig. 15 - Nontoxic adenoma of the thyroid. The alveoli are small and are surrounded by abundant stroma. Hyperthyroidism develops in about 25 per cent of these cases.

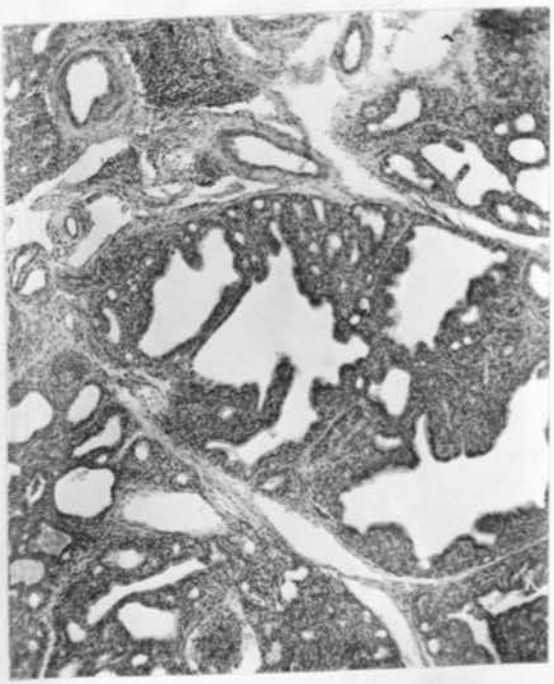

Fig. 16 - Exophthalmic goiter. Showing marked irregularity of the alveoli and the increased stroma.

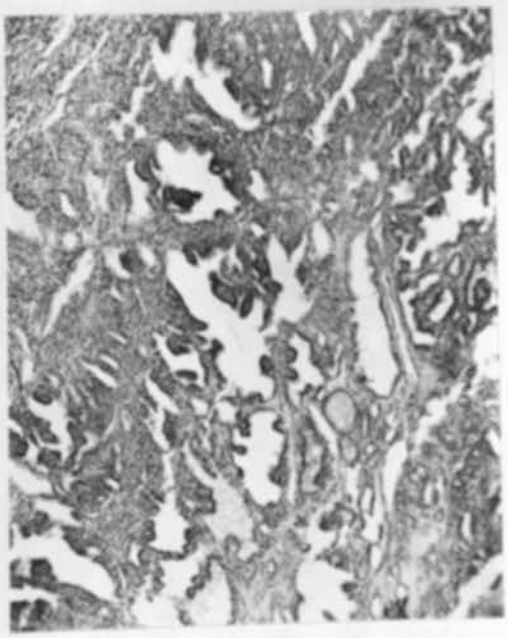

Fig. 17 - "Cured by X-ray". This case gave a five-year history of exophthalmic goiter. Many x-ray treatments had been given and a cure supposedly obtained. Persistent symptoms of hyperthyroidism and the evidence of hyperplasia show that a cure was not obtained.

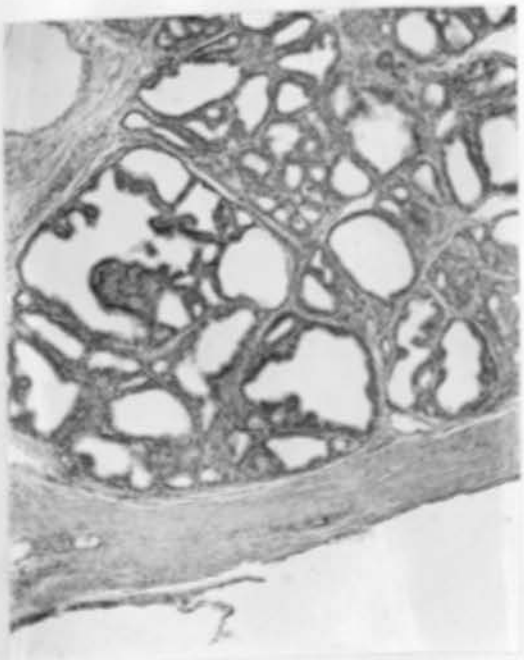

Fig. 18 - Exophthalmic goiter. The alveoli are almost devoid of colloid.

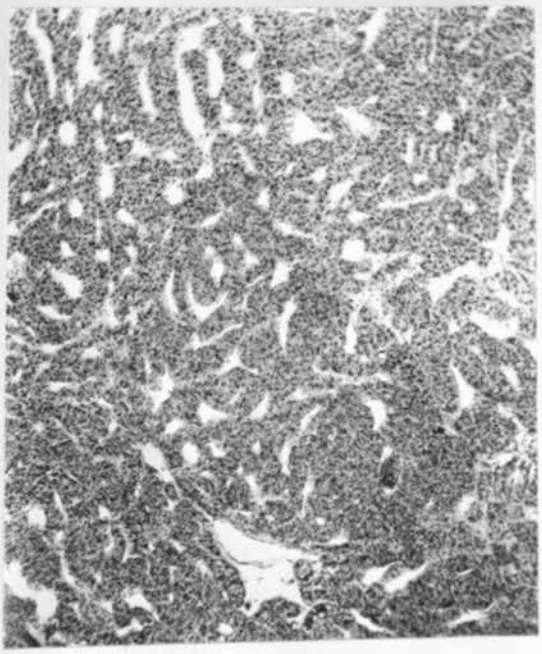

Fig. 19 - Carcinoma of the thyroid.

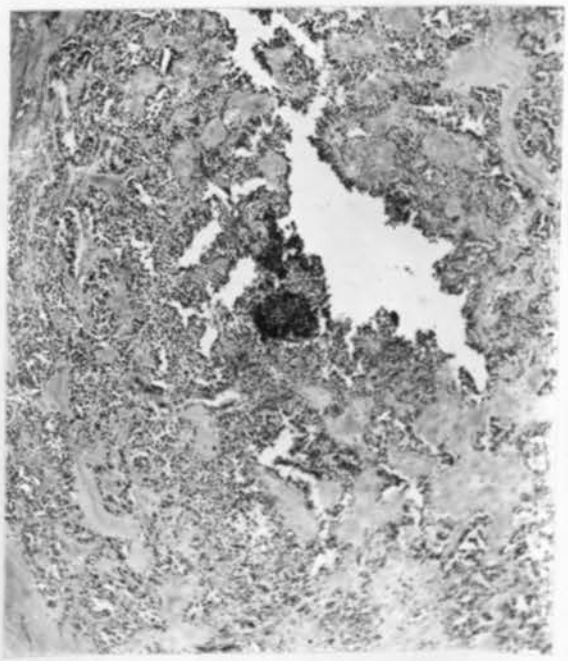

Fig. 20 - Carcinoma of the thyroid.

Fig. 21 -Colloid and fetal adenoma of the thyroid.

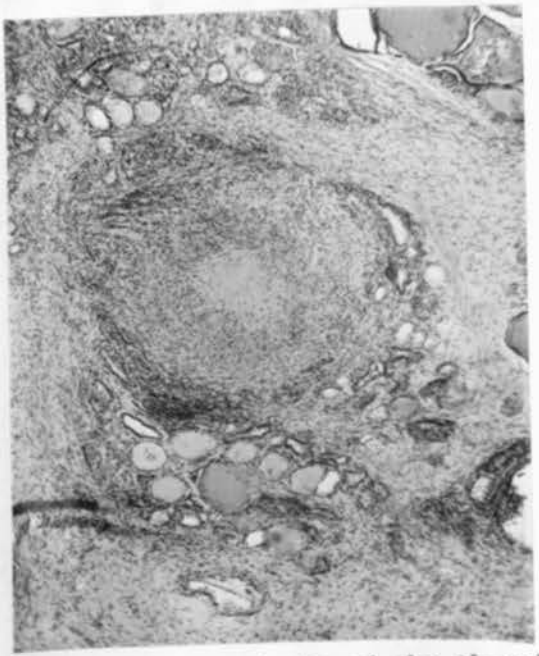

Fig. 22 -Tuberculosis of the thyroid. Showing a large caseating tubercle.

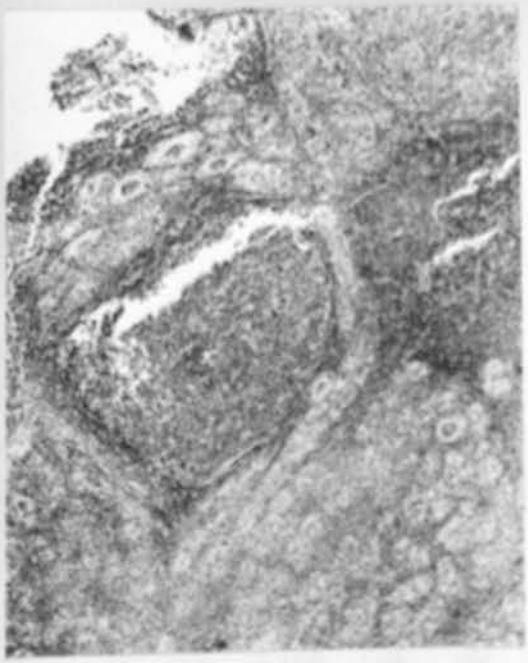

Fig. 23 - Diffuse thyroiditis

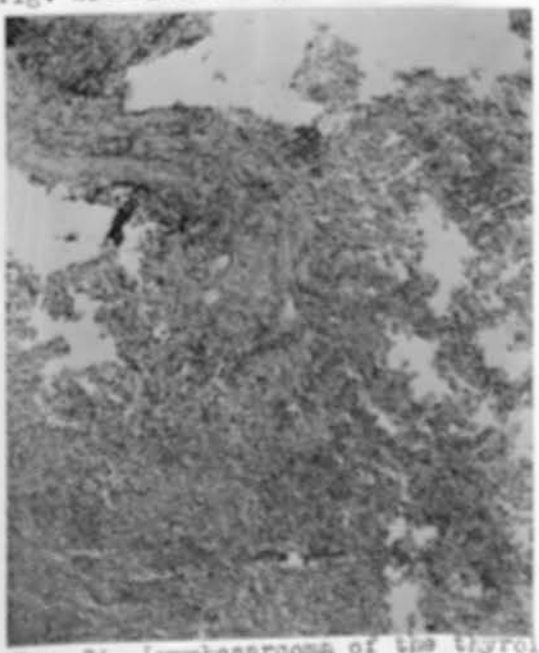

Fig. 24 - Lymphosarcoma of the thyroid.

Fig. 25 - Steps in the operation of thyroidectomy. The skin and platysma have been divided and the flap retracted. Clamps have been applied and the muscles are about to be divided.

Fig. 26 - Steps in the operation of thyroidectomy. The muscles have been divided on one side and are being retracted on the opposite side. Reflection of the cervical fascia and the capsule has begun.

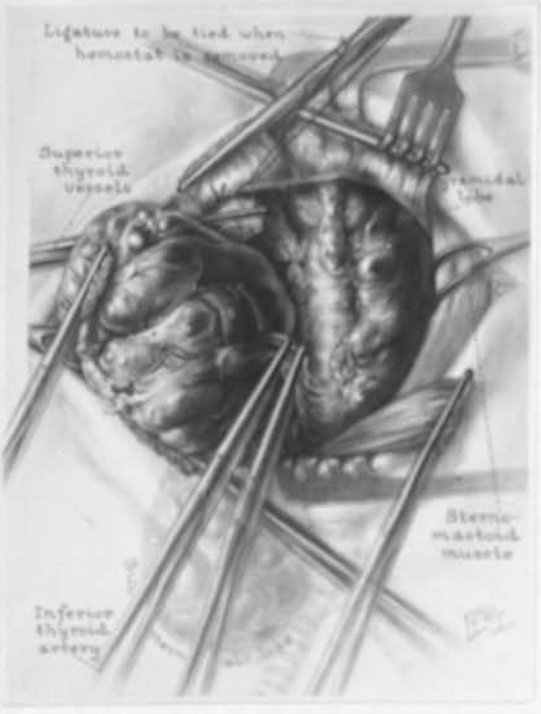

Fig. 27 - Steps in the operation of thyroidectomy. Right superior pole of gland freed and isthmus divided. Medial branch of interior thyroid artery ready to be divided.

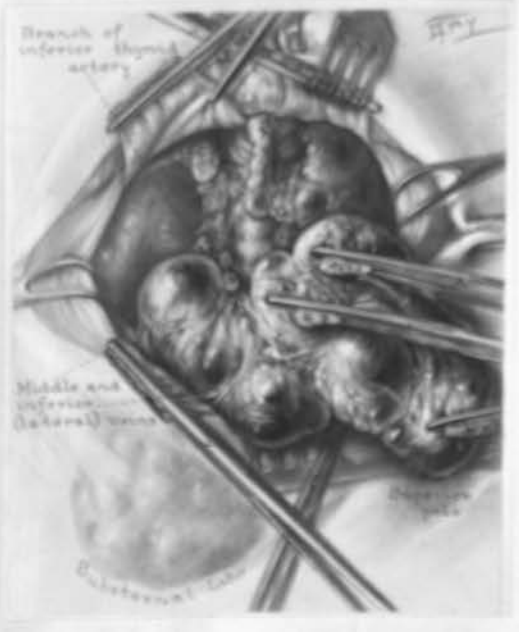

Fig. 28 - Steps in the operation of thyroidectomy. Gland drawn downward and inward, both branches of the inferior thyroid artery have been divided and ligated. The middle and inferior thyroid veins are exposed for division.

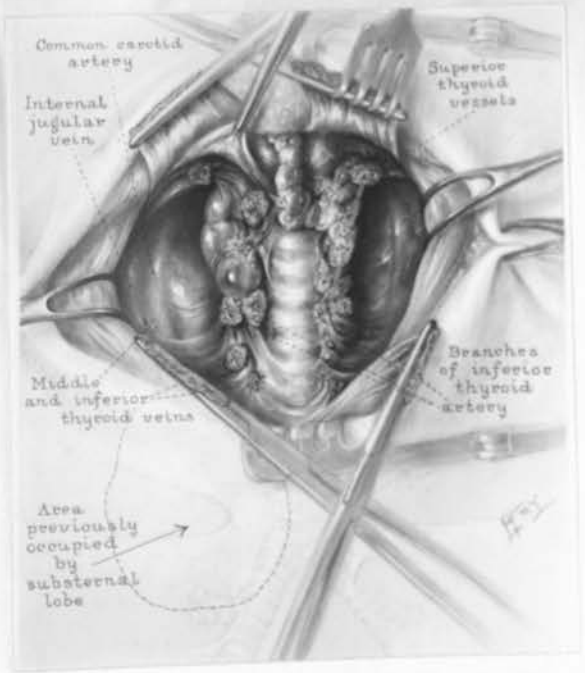

Fig. 29 - Steps in the operation of thyroidectomy. Operation completed except the suturing of divided muscles and closure of skin incision.

Fig. 30 - Steps in the operation of thyroidectomy. The muscles have been sutured. The drainage tube is in place and the skin is ready for suturing.

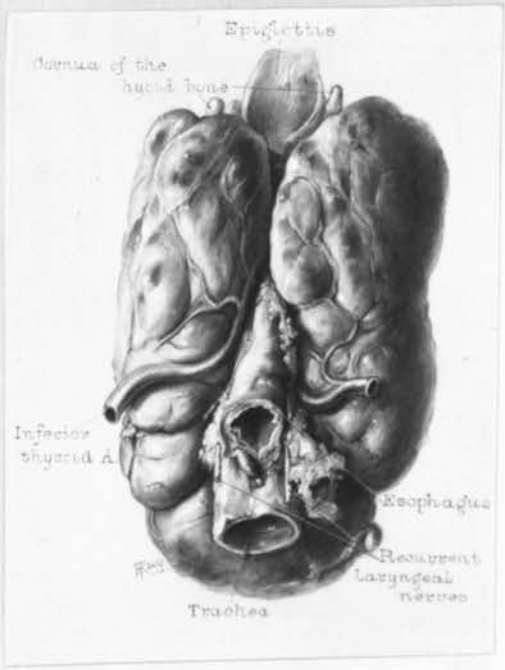

Fig. 31 - Posterior view of thyroid gland surrounding trachea and esophagus.

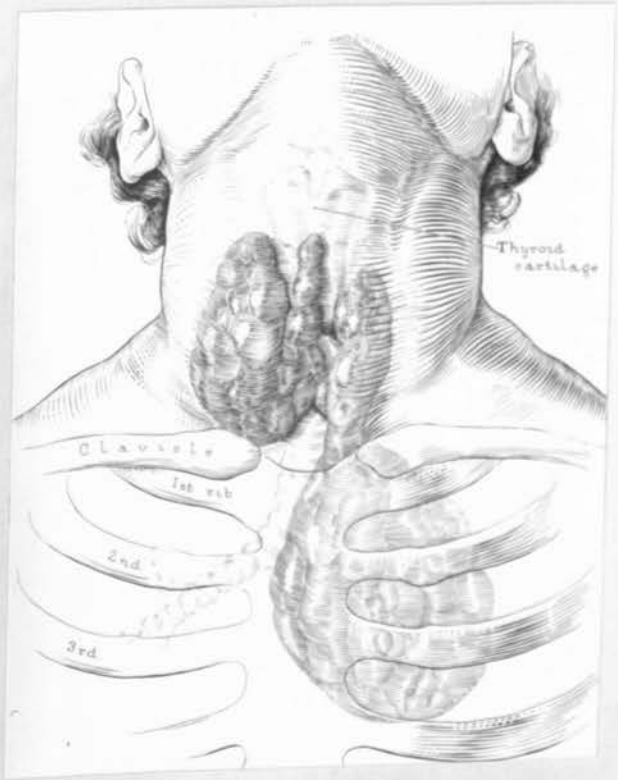

Fig. 32 - Diagram showing huge adenomatous intrathoracic projection from the lower pole of the left lobe of the thyroid.

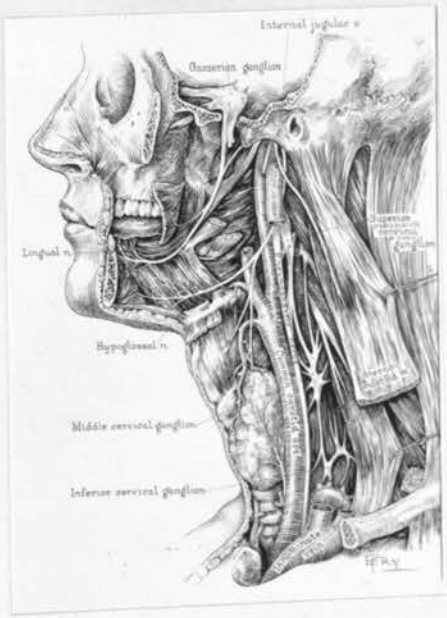

Fig. 33 - Showing the blood and nerve supply of the thyroid gland.

Fig. 34 - Showing the position of a substernal goiter.