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Nodular goiter : the correlation of its pathological with its clinical picture

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N O D U L A R G O I T E R

The Correlation of Its Pathological With Its Clinical Picture

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"If the thyroid were guilty of all the ills it has been accused of and performed all the functions that have been ascribed to it, it would without doubt be at the same time one of our greatest malefactors as well as one of our greatest benefactors."

Marine (43)

INTRODUCTION

Why should a gland that presumably liberates only one hormone produce two different clinical entities when it hyperfunctions? This is a perplexing question and one which has not been explained to my satisfaction in any of the courses in medical college. Of course, there is much or possibly most of our medical knowledge that we must take on the weight of authority and not question too deeply else we, as students, would be foundered in a sea of confused thought and opposing ideas.

I have set as my goal in writing this thesis the correlation of the pathology of nodular goiter with the clinical symptoms produced by it. A utilitarian classification of goiter is also sought. Most important to me, my aim is to bring order out of the turmoil produced in my mind by reading the conflicting opinions of the various authorities on goiter. To use an old but apt chestnut, I want something I can "hang my hat on".

The phenomenon of exophthalmos will not be discussed as its exact relation to the thyroid is in dispute and it would only confuse the issue more.

Strumitis, or thyroiditis, will not be discussed. Malignancy of the thyroid will only be mentioned as it applies to the problem at hand.

I wish to thank Dr. J. Perry Tollman for his advice as to the approach to my problem, and Dr. Charles P. Baker for his criticism and suggestions as to the fashioning of the finished product. I further wish to state that the conclusions reached are not necessarily in accord with the ideas of my sponsors.

HISTORICAL

In providing a synopsis of the history of goiter I have called heavily upon articles by Mayo (51) and Panebaker (62). The latter's article was especially good and his phraseology was particularly apt in his introductory paragraph which will follow.

"For thousands of years goiter has been a familiar malady. An unsightly and frequently fatal disease, it was accepted as an inoperable affliction in communities where it prevailed, and paraded the streets exciting the curiosity of the populace in towns where it was unusual. The patient sought relief from suffocation, difficulty in swallowing, failure of the heart and from a distressing disfigurement. Thus this conspicuous tumor of the throat was a perpetual challenge to the physician, a perplexing problem to the surgeon."

The ancients failed to differentiate the thyroid from other cervical glands. This confusion reigned through the Middle Ages when goiter was confounded with scrofula and other disease of the glands of the neck.

Galen had found the gland and believed it to be an accessory gland to the larynx and pharynx. Celsus in 45 A.D. removed a goiter which he described. Mayo

believes that the tumor was a swelling of one of the cervical glands, whereas Panebaker interpreted it to be a cystic goiter. Albucasis (330 A.D.) undertook an operation for true goiter, controlling hemorrhage by ligature and hot iron. Down to Paulus Aeginata (625-690 A.D.), the last great representative of ancient medical science, Greek and Roman physicians used the term "bronchocele" for goiter. The popular Latin terms were "tumor gutturis" or "gutter tumidum". Tumors of the lymphatic glands were called "strumae".

Vesalius and his successor Realdus Columbus of Padua (1550) described and threw more light on the structure of the thyroid. Eustachius, professor of anatomy in Rome, discovered the isthmus of the human thyroid. Fabricus of Aquapendente was the first to discover that goiter was a tumor of the thyroid.

The first monograph concerning the thyroid was written by Thomas Wharton (Adenographia, London, 1656). He was also the first to employ the term "thyreodea".

The ancient treatment of goiter was applications of plasters usually containing a resin or sea-salt. Other therapy included the daily washing of the neck with sea water. Later, the spongiae marinae ustae were favorite remedies. The hard, cancerous, or vascular

goiter was considered incurable.

Felix Platter, professor of medicine in Basle, was the first to write on endemic cretinism in the latter half of the sixteenth century. Shortly afterwards, Josef Simler of Zurich also gave an account of the cretins of Valais.

In the opening years of the 18th century Forester, Fulvius Gherli, Petit, Roonhuysen, Hoin, and Conrad Ludwig Walther were reported to have excised true goiters. Mayo, on examination of the literature, finds only two cases which might be considered as goiter.

Horace de Saussure in the latter half of the 18th century wrote that cretinism occurs in valleys below an elevation of 3000 feet above the level of the Mediterranean. The cause he believed was the heat and stagnation of the air which is shut in by the surrounding mountains. The heated and infected air acts principally upon the tender fibres of the infant producing considerable relaxation from which results the general atony characteristic of the condition.

In 1792 appeared Fodere's classic work on cretinism which he claimed occured on an hereditary basis. He believed that goitrous parents produced cretins and that there were goitrous persons before there were cretins.

Interbreeding he believed caused the high development of the cretin characteristics as seen in the Swiss valleys.

George Murray (1891) introduced the treatment of cretinism with the thyroid gland of a sheep.

Baumann (1895) furnished the first definite information on the chemistry of the thyroid when he wrote that iodine is a normal constituent of the gland. However, iodine had been used knowingly in the therapy of goiter since Coindet accidently stumbled onto it in 1820.

In 1917 Marine and Kimball started giving two grams of sodium iodide over a two week period each Spring and Fall to public school children in Akron, Ohio, as a preventative for endemic goiter. This plan was put into practice in Zurich the next year where five milligrams of iodine were given to each child every week the year around.

In the surgical treatment of goiter Theodore Kocher of Bern (1841-1917) stands out as the first great thyroid surgeon. In his paper published in 1883 he standardized the operation of lobectomy and reported 240 cases of non-malignant goiter which he operated with a mortality of 11.6 per cent. However, later

after the performance of 2,000 thyroidectomies he had a mortality of only 4½ per cent.

Kocher was not the first, as mentioned before, to do thyroid surgery. At the end of the 18th century when the first triumphs of the surgical treatment of goiter were being celebrated in Germany, it was condemned in rrance by all the members of the Academy of Surgeons of Paris except Desault who was the first Frenchman to whom excision of a struma was accredited.

Around 1850 Luigi Porta first defined and recommended the operation of enucleation and resection for thyroid adenoma. Sick in 1867 was perhaps the first to perform successfully a total lobectomy.

No history of the thyroid and its diseases would be complete without mention of that triumvirate of physicians who did so much to define the disease of thyrotoxicosis and its symptoms. These men were a Scotchman -- Parry, an Irishman -- Graves, and a German -- Basedow.

Caleb Hillier Parry (1755-1822) had in his posthumous papers, published in 1825, an article titled Enlargement of the Thyroid Gland in Connection with Enlargement or Palpitation of the Heart. This report was based entirely upon his own observations.

Robert James Graves (1797-1853) was born in Dublin and studied in England and on the continent. He returned to Dublin to set up his own private medical school. In 1843 he published his System of Medicine in which he described in detail the symptomatology and physical findings in exophthalmic goiter.

Carl Adolphus von Basedow published the first complete monograph on exophthalmic goiter in 1840. In it he accurately cited the symptoms of the disease. Although he was often wrong in his conclusions credit must be given to his thorough-going study of the pathological physiology of the thyroid gland.

One might conclude from the above survey of great men and events in the history of goiter that all of the important work has been done by Europeans. This is not true. The history of thyroid research is not a dead thing. It is still going on and will be for some time if the men who are now working on the problem continue to try to prove their theories of the pathology and correlative clinical findings in goiter. You will be introduced to the outstanding American clinicians and pathologists in the following pages.

THE GLAND

Before delving into the controversial literature concerning dysfunction of the thyroid, let us look at the gland as a normally functioning endocrine organ.

Development

Means (54) states that "phylogeny is of more fundamental significance (than ontogeny)" in the development of the thyroid gland. This gland antedates all other endocrine organs except the gonads. The thyroid ancestrally belongs to the alimentary tract. It was originally a gland taking part in digestion, a function lost long since but which ontogeny still recalls.

In the human being the thyroid gland arises from the floor of the pharynx in the region between the first and second pharyngeal grooves as early as the third week of fetal life. It arises as an epiblast-lined diverticulum which by the end of the fourth week has become a sac attached to the pharynx by a tubular neck. This neck which is known as the thyroglossal duct normally atrophies during the sixth week, but its point of origin on the tongue is permanently indicated by the dimpled foramen cecum. Simultaneously, the thyroid loses its lumen and is converted into solid

epithelial plates. The gland then becomes crescentic in shape and ultimately settles to a transverse position on each side of the trachea.

In the eighth week follicles begin to appear. Follicle formation starts, according to Norris (59) (1916), as a concentric orientation of cells within the plates. Many mitoses are observed at this stage and the plates become studded with many little follicles, the anlagen of the future follicles. The cells become larger. By eleven weeks, the plates and bars have broken up into solid masses of cells a few of which possess lumina. As the lumina first appear, they have no visible contents. Colloid is first seen at the eleventh week.

The height of the epithelium in the fetus is not very different in the fetus and adult. It is the quantity of stored colloid and the total number of cells comprising the follicle which increase as development proceeds.

At birth, the thyroid is probably fully functioning as indicated by its histology and chemical composition. The iodine content is an index of its hormone content. The concentration gradually increases from birth and reaches a maximum at about the age of 40.

Anatomy

The Germans call the thyroid the shield gland (Shilddrüse). Their reason for such a name probably lies in the situation of the thyroid which is placed in front of the larynx and trachea to both of which it is moulded. It is the largest solely endocrine organ in the adult. In a child the thymus is larger.

The thyroid gland is a highly vascular organ, situated at the front and sides of the neck; it consists of right and left lobes connected across the midline by a narrow portion, the isthmus. Its weight is somewhat variable, averaging about 25 grams. It is slightly heavier in the female.

The lobes are conical in shape, the apex of each being directed upward and lateralward as far as the junction of the middle with the lower third of the thyroid cartilage; the base looks downward, and is on a level with the lower fifth or sixth tracheal ring. Each lobe is about five centimeters long; its greatest width is about three centimeters, and its thickness is about two centimeters. The lateral or superficial surface is convex, and covered by the skin, the superficial and deep fasciae, the Sternocleidomastoideus, the superior belly of the Omohyoideus, the Sternohyoideus, and

Sternothyroideus, and beneath the last muscle by the pretracheal layer of the deep fascia, which forms a capsule for the gland. The deep or medial surface is moulded over the underlying structures, viz., the thyroid and cricoid cartilages, the trachea, the Constrictor pharyngis inferior and posterior part of the Cricothyreodeus, the esophagus, the superior and inferior thyroid arteries, and the recurrent nerves. The anterior border is thin, and inclines obliquely from above downward toward the middle line of the neck, while the posterior border is thick and overlaps the common carotid artery, and, as a rule, the parathyroids.

The isthmus connects together the lower thirds of the lobes; it measures about 1.25 centimeters in breadth, and the same in depth, and usually covers the second and third rings of the trachea. Across its upper border runs an anastomotic branch uniting the two superior thyroid arteries; at its lower border are the inferior thyroid veins. Sometimes the isthmus is altogether wanting.

A third lobe, of conical shape, called the pyramidal lobe, frequently arises from the upper part of the isthmus, or from the adjacent portion of either lobe, but most commonly the left, and ascends as far

as the hyoid bone.

The arteries supplying the thyroid gland are the superior and inferior thyroids and sometimes an additional branch (thyroidea ima) from the innominate artery or the arch of the aorta, which ascends upon the front of the trachea. Major (41), writing in 1909, stated that the blood vessels branch to form a network on the surface of the gland from which are sent penetrating vessels which arborize among the follicles ending in a follicular artery about .0125 millimeters in diameter. This in turn breaks up into a rich cappillary network around the follicle. On the opposite side of the follicle, the vein arises and retraces the arterial pathway. The veins form a plexus on the surface of the gland and on the front of the trachea; from this plexus the superior, middle, and inferior thyroid veins arise; the superior and middle empty into the internal jugular veins; the inferior, into the innominate vein.

The lymphatic vessels run in the interlobular connective tissue, not uncommonly surrounding the arteries which they accompany, and communicate with a net-work in the capsule of the gland. The concentration of hormone in lymph and blood leaving the gland are about

equal, but the latter has the most volume and is thus the most important channel.

The nerves to the gland are derived from the middle and inferior cervical ganglia of the thoraco-lumbar autonomic system. The function of these nerves in the economy of the thyroid is problematical.

Histology

The normal histological picture presented by the thyroid varies considerably at different ages, in different countries, and at different altitudes. As Joll (30) states, "It seems certain that appearances which are legitimately regarded as within physiological limits in certain localities should be interpreted as bordering on the pathological in others." This plays havoc with any discussion of thyroid histology whether it be concerned with normal or pathological microanatomy.

The thyroid gland is composed of two elements: (1) the supporting structure or stroma; and (2) the secretory or parenchymatous portions.

The connective tissue stroma envelopes the gland completely as a thin and almost transparent layer and constitutes its true capsule. The capsule is continuous with numerous bands of connective tissue forming septa which pass from its deep surface into the sub-

stance of the gland and break up the parenchyma into its characteristic structure. According to Rienhoff (73) there is no true lobular system in the thyroid, but the main mass of the gland is divided and subdivided into connecting "bars, bands, plates, stalks, and bulbs" of parenchyma. Wilson (87) was the first to deny the lobular structure of the thyroid.

The "acini. . . may be considered from both the structural and functional point of view to be the primary, or secretory, unit of the organ in question. The cells of the follicle are makers of the hormone; their lumina, the warehouse where it is stored." Means (55).

In normal adult life the follicles are roughly spherical in shape and vary considerably in size. The average diameter of each follicle is in the neighborhood of 500 micron. The normal range is from 30 to 1294 micron. Each is a closed vesicle with an epithelial lining and a lumen occupied by a stainable substance, colloid. The epithelial lining rests on a layer of fine connective tissue fibrils in which capillaries, lymphatics, and nerves are embedded. There is no true basement membrane.

The epithelium forms a continuous lining for the

acinus, arranged in a single layer. Each cell is of the cuboidal type, although the shape varies somewhat at different ages and in different phases of activity of the gland. The height of the epithelium seems to be a fair index as to its activity.

The individual thyroid parenchymal cell is similar to many other gland cells. It contains a large, translucent, reticulated nucleus and its cytoplasm presents a complicated and variegated structure. In 1916, Bensley (4) observed that under excitation by iodine the cells could be seen to be filling up with colloid and discharging it into the lumen of the follicle. The cells possess mitochondria which are arranged parallel to the long axis of the cell. Goetsch (23) and Cramer and Ludford (16) regard them as valuable guides to the secretory activity of the epithelium, since they are much more conspicuous during active secretion. The latter writers concluded that changes in the form of the mitochondria were means by which the cell could create a tremendous surface within itself for the adsorption of intracellular lipoids. This flow of lipoids would alter the concentration of fats in the cytoplasm and cell membrane which would account for alterations in cell permeability and hence in the cell-environment

relationship. The Golgi apparatus can also be found in the epithelial cells by special staining methods.

The presence of inter-follicular epithelium is highly debatable and Rienhoff's (73) precise work seems to deny it. Lymphocytes are frequently found in the interstitial tissue, but definite lymph nodes are rare.

Colloid is usually found filling the follicles and very few ones are found in the normal gland. Peripheral vacuoles are often noticed and it has been suggested that these are due to resorption of colloid by the cells.

Colloid stains uniformly with acid dyes. The active principle of the thyroid secretion is almost certainly contained in the colloid. Its absorption and transportation, as mentioned before, seems to be predominantly by the blood stream. Carlson and Woelfel (10) in 1910 found the thyroid colloid unique. It is "the only substance in the whole animal kingdom where a supposed physiological secretion is first eliminated from cells in one direction, the absorbed by the same cells and eliminated in the reverse direction. This process resembles that of formation, resolution and absorption of pathological exudates or transudates, or

removal of intracellular by-products and waste products."

In both mammals and birds, after removal of a part of the gland, the remainder undergoes regeneration. The degree of regeneration, according to Joll(30), depends upon the amount of gland removed, the amount of iodine provided in the diet, the nature of the diet, the age, nutritional state, sexual activity, and the time of year. If the amount of gland removed be small, no change occurs in what remains; as the amount of gland removed is increased colloid storage occurs in the portion conserved; and finally when very little thyroid tissue is preserved active hyperplasia follows in the remaining fraction. Anatomically, the changes in the thyroid remnant are exactly similar to the hyperplastic changes found in certain goiters.

Physiology and Chemistry

The thyroid gland is an organ which has a characteristic epithelial structure. It produces a physiologically active secretion which is elaborated from substances reaching it by way of the blood stream, and, in turn, passes this secretion into the general circulation. It is thus an organ or gland of internal secretion.

The exact nature of the thyroid secretion has not been determined, nor has it been firmly established whether there is more than one specific secretion. It is generally assumed that the internal secretion of the thyroid is of the nature of a hormone, or chemical messenger, in contradistinction to the enzymes which are produced by most organs of external secretion.

There are three general methods by which the thyroid function has been studied:

(1) By observing the effects of the removal of the gland in experimental animals and in man, and comparing these results with those which occur when the thyroid is absent or destroyed by disease. Basinger (2), in 1916, described sporadic cretinism produced by ablation of the thyroid in animals. In young people it is known that an atrophy of the thyroid gland is associated with an arrested mental development along with stunted growth and the characteristic facies of sporadic cretinism. In adults as a result of surgical extirpation or atrophy of the thyroid there ensues a state of chronic malnutrition, loss of hair, emaciation, edema of the skin, and mental degeneration, a condition known as myxedema when occuring spontaneously or cachexia thyreopriva when occuring as the result of surgery.

(2) By feeding thyroidless animals on thyroid gland tissue, fresh or dried, or administering physiologically-active extracts of the whole gland, and comparing these results with those in normal controls. Murray (58), in 1891, published the first case of myxedema successfully treated by hypodermic injections of a glycerin extract of the fresh thyroid gland of a sheep. With thyroid medication in post-operative myxedema the result is a perfect or almost perfect restoration of function, while in myxedema due to atrophy and disease of the gland it is usually, though not invariably satisfactory. In normal persons moderate doses of thyroid causes a fall in blood pressure. Large doses cause tachycardia, arrhythmia, nervousness, flushing of the skin, muscular weakness, pains in the joints, and increased perspiration.

(3) By chemical investigations of the gland to isolate, identify chemically, and estimate the activity, in thyroidless and in healthy animals of the specific physiological substance or substances which constitute the thyroid hormone or hormones. In 1896 Bauman demonstrated that iodine was contained in the thyroid gland in combination with a protein globulin which he called thyreoglobulin. This combination contained 9.3 per cent

of iodine by dry weight. In 1914, Kendall (32) isolated a white crystalline compound from the thyroid gland containing 65 per cent iodine, which he called thyroxin. Harrington (27), in 1926, concluded that the correct empiric formula of thyroxin is $C_{15}H_{11}O_4NI_4$, making it highly probable that thyroxin is a tetraiodo substituted derivative of the p-hydroxyphenyl ether of tyrosin. An experimental and clinical comparison of the physiologic activity of dessicated thyroid and thyroxin are identical. The thyroid contains about one-fifth of all the iodine in the body. It is the body's only storage depot for iodine and rapidly traps any extra iodine entering the organism up to the height of its capacity which in the normal gland might be as much as 23 milligrams. According to Marine (46) (47), the thyroid gland's affinity for iodine, both in vivo and in vitro, distinguishes it from all other tissues. Uhlenhuth (82) proved, by administration of known quantities of thyroxin and inorganic iodine to larvae of the tiger salamander, that inorganic iodine as such is not the active principle of the thyroid hormone. Very small doses of thyroxin in the water caused metamorphosis in 13 days, whereas a dose of inorganic iodine, at least eighty times larger, in the water and feeding

some by mouth in addition did not produce this result.

The Hormone

Thyroxin is a crystalline iodine compound, melting at from 210° C. to 250° C. under varying rates of heating. It produces qualitatively all the physiological actions of dried thyroid gland, but when compared with the latter on the basis of iodine content it is quantitatively rather weaker. Kendall and Simonsen (33) showed that both dried thyroid gland and iodothyrine, while they possess the biological properties of the thyroid gland, may, when treated by appropriate chemical methods, fail to yield any thyroxin, thus conclusively proving that thyroxin is not essential to the production of normal thyroid activity. It has also been shown that thyroxin, unlike iodothyroglobulin, does not increase the reactivity of the vago-sympathetic system, nor does it have any effect on an isolated strip of intestinal muscle.

Means (55) lists the following actions of the thyroid hormone:

(1) Calorigenic Action -- it increases the rate of oxidation of tissue cells.

(2) Action upon Growth, Maturation, and Differentiation of tissues.

(3) Action upon Distribution of Body Water, Salts, and Colloids -- when the organism is deprived of thyroid hormone, along with a decline in the rate of oxidation, there takes place a storage of water, salts, and protein. In hypothyroid states there is reduction of plasma volume and an increase in concentration of plasma protein and spinal fluid protein. Both of these fluids revert to normal composition when thyroid is given.

(4) Action upon Carbohydrate Metabolism -- appears to promote glycogenolysis and to inhibit glycogen formation and storage.

(5) Action upon the Nervous System -- excess increases, scarcity decreases irritability and reaction time. An excess of the hormone increases vasomotor activity, peristaltic activity, and activity of sweat glands.

(6) Action upon the Circulatory System -- a secondary effect accounted for under the previous headings.

(7) Action upon the Muscular System -- similar to action on nervous system or oxidative action in general.

(8) Action upon other Endocrines -- has a non-specific action upon the other glands, the same as upon other cells in the body.

Anterior Pituitary -- On ablation of the pituitary, the

thyroid hypofunctions; but there is not a full-blown athyreosis. The thyrotropic hormone stimulates the thyroid to intense hyperplasia, purges it of stored colloid, and produces thyrotoxicosis with the thyroid as the mediator. After the thyroid has responded to the thyrotropic hormone for a certain time it ceases to be able to do so. Having passed through a period of hyperplasia, the gland passes on to one of involution or rest.

Posterior Pituitary -- there seems to be an interrelationship between the thyroid and the posterior pituitary and this may be the means by which the thyroid mediates its diuretic action.

Pancreatic Islets -- diabetes mellitus is aggravated by hyperthyroidism and diminished by the absence of thyroid. The exact mechanism of this action is unknown.

Adrenal Cortex and Medulla, Thymus, Gonads, and Parathyroids -- the interrelationships are obscure and highly debatable.

GOITER

Before nodular goiter is discussed, the term goiter should be defined. In order to prevent confusion and also because of its seeming close relationship to nodular goiter, the definition will be of simple goiter without toxic manifestations. A simple goiter is any enlargement of the thyroid gland which is neither inflammatory nor malignant, and not associated with toxic features. This definition is open to some criticism inasmuch as it is sometimes difficult to distinguish between a goiter producing toxic symptoms and one free from such, or to distinguish benign from malignant adenomata.

Marine (43), who has done much original research into the problem of simple goiter and whose ideas are generally accepted, states that simple goiter is primarily a disease caused by iodine deficiency.

It has a seasonal variation, developing more frequently during the winter and early spring months. This seems to parallel the seasonal variation in the storage of iodine by the thyroid as found by Seidell and Fenger (75).

The most important endemic areas in North America,

as mapped by Marine (43), are the St. Lawrence River and Great Lakes basin, extending west through Minnesota, the Dakotas and adjacent Canadian provinces and also the Pacific Northwest, including Oregon, Washington, and British Columbia. The less important foci occur throughout the Appalachian Mountain region, the Rocky Mountain states, and states in the Great Central Basin. Most of these regions are mountainous, although there are numerous exceptions. Of greater importance is the occurence for the most part in soils deposited from the glacial period.

Beginning at about the age of puberty, females are more often affected than males. In the severest endemic regions this occurence is masked. The periods of life when simple goiter most frequently develops are during fetal life, during pregnancy and lactation, during puberty, and during the menopause.

The relation of iodine to the structure of the thyroid in normal glands in developing and involuting hyperplasia was first extensively investigated by Marine and Williams (50) in 1908, and Marine and Lenhart (48) (49) in 1909. In thyroids with normal structure the iodine contents varied between 5.5 and 1 milligrams per gram of dried gland. When the store

of iodine was below 0.1 per cent, hypertrophic and hyperplastic changes were regularly found. The degree of hyperplasia varied inversely with the iodine store; so that in the most marked hyperplasias, iodine was absent or present only in traces.

McCarrison (53) has produced goiters in animals (pigeons, rats, and goats) under experimental conditions. He incited hypertrophic goiters by massive doses of fecal bacteria in admixture with their food, producing congenital goiter and cretinism in their offspring. Hyperplastic goiter was provoked by an excess of fats or fatty acids in an otherwise well-balanced diet. The colloid goiter could not be exactly reproduced, but was simulated in animals ingesting an excess of lime in an otherwise well-balanced diet. With the exception of those produced by fecal material, the above goiters were preventable by increasing the intake of iodine proportionately. He then produced in animals receiving diets rich in white flour and adequate in iodine and minerals but barren of green vegetables and fruit a new type of goiter resembling primary Graves' disease, described it as a heterotrophy. The principal cause of the goiter was vitamin B deficiency. Along with the avitaminosis he suggested

several other factors in the production of this type of goiter. Among these were inefficiency of the thyroid brought about by its malnutrition with impediment to the normal revolution of its cycle of activity, imperfect metabolism in body fluids and tissues causing depletion of the thyroid hormone necessary for their combustion, and a physiologically subnormal or pathological alimentary tract whence bacterial agents or their toxins may find their way into the circulation and induce pathological changes in the thyroid gland. This goiter could not be prevented by additional provision of iodine, but could be by a well-balanced, vitamin-rich diet.

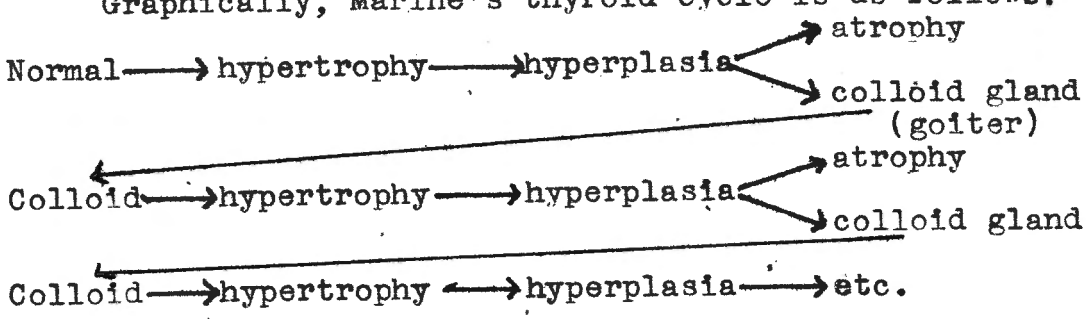
Certain underlying or secondary factors contributing to the production of endemic goiter were found by Oleson (61) in a study conducted in the Cincinnati area. He found deficiency or absence of iodine to be undeniably the immediate cause of this condition. The secondary factors were infections, intoxications, faulty food habits, and demands for extra iodine in certain epochs of female life. Lunde (38), studying endemic goiter in Norway, found the quantity of iodine excreted through the urine in adult males in Norwegian goitrous districts to be approximately in inverse ratio to the

incidence of goiter among the school children in the same districts. He recommended iodine in natural organic combinations, such as sea-fish, as the best prophylaxis and believed that ionized iodine might induce toxic change in endemic goiter -- so-called Jod-Basedow or Iod-Basedow. Marine (45), in 1910, found that even the fish and land animals in endemic areas had enlarged thyroids.

The thyroid has a cyclic response to stress according to Marine (43). The gland cells begin to hypertrophy when the iodine store falls below a given level, less than 0.1 per cent, and continue this hypertrophy and hyperplasia until exhaustion atrophy or recovery supervenes. Anatomical recovery refers to the involution of the active hyperplasia to the colloid or resting stage. He considers the colloid goiter to be the nearest to normal, both anatomically and chemically, that a thyroid gland which has once been in a state of active hyperplasia can assume. In lower animals with the exception of the rat, this hyperplasia is regular and uniform, while in man it is frequently irregular and nodular -- so-called struma nodosa or adenomatous goiter. These growths (42) are functionally active yet have certain of the attributes of

tumor, one of which is that their growth once initiated is not controlled by iodine as is every simple hyperplasia.

Graphically, Marine's thyroid cycle is as follows:



NODULAR GOITER

Nodular goiter is a goiter with little swellings which are discrete from the rest of the gland, according to Means (55). That is a fairly safe definition inasmuch as no mention is made of whether the "swellings" are neoplastic or whether they are the result of a thyroid dysfunction. Even in such a simple and incomplete definition one runs into difficulty, however, with the word "swellings". Hellwig (28), Broders (8), and MacCarty (40) seem to admit of no difference between single or multiple swellings in their classification of nodular goiter. Possibly a better definition, and one sufficiently loose to permit of no particular argument, would be: Nodular goiter is a goiter containing single or multiple nodules which are discrete from the rest of the gland.

From this rather equivocal definition we can proceed to analyze the opinions of clinicians and pathologists. Since this paper is not primarily concerned with the clinical aspects of the nodular goiter problem, the ordinary sequence of discussion of a medical subject will not be followed. The pathological picture of the various types of nodules is agreed upon

by most observers, but it is in the interpretation of this picture that the observers fall into dispute.

Pathology

Joll's (30) description of the types of nodules and their gross and microscopic appearance is in agreement with most observers and therefor his descriptions will be followed for the sake of convenience. When the whole gland is small, careful palpation is needed to detect the nodules, or they may be found only on cutting the gland open; in most cases the irregular outline of the gland indicates its nature. The nodules may develop very strikingly in one lower pole, and as a result a large mass may be formed extending downwards into the thorax; if this tumor possesses only a narrow pedicle it may form a true intrathoracic goiter. Formation of large nodules in the upper poles is more rare. Pendulous tumors may form from the thinning and splitting of the infra-hyoid muscles allowing the mass to protrude. Retropharyngeal, retroesophageal, retrolaryngeal, and retrotracheal extensions of the goiter may result from irregular development of one or more of the nodules.

On section, macroscopically, the nodules vary according to the stage of the disease. An increase in

connective tissue is always found. This may be very conspicuous, forming a tough, fibrous framework between the nodular masses of which the gland is composed; or it may even be so tough as to resemble cartilage in texture, and calcareous deposits or actual bone formation may occur within its substance. The arteries often show the changes of endarteritis obliterans.

The nodules enclosed by the fibrous septa may be of uniform size, but far more often there is a wide variation in size. The nodules may be of a pale yellowish-pink, semi-translucent appearance, indicating a colloid structure. Degenerative changes are common especially in the larger nodules. Hemorrhages are common, resulting in patches of a deep red or orange color. Cyst formation is frequent with the wall usually of ragged adenomatous tissue, though in some instances it may be quite smooth. In most cysts the contents are watery and brownish, but clear fluid or gelatinous colloid material is sometimes found. Large nodules often show a conspicuous, radiating, scar-like mass of fibrous or hyaline tissue near the center, due to the imperfect blood supply.

Microscopically, the stroma shows great overgrowth

of the fibrous elements, and hyaline and calcareous, or even osteoid, changes occur in it. The structure of the nodules varies widely, both within the individual nodules and in different nodules found in each goiter.

The follicles are often of enormous size, lined with flattened epithelial cells, show little evidence of secretory activity, and contain deeply staining colloid. The peripheral follicles tend to be smaller than those nearer the center of the mass. The fibrous tissue which delimits the nodules contains in its meshes flattened and atrophic follicles.

Other nodules may contain no colloid, the cells being arranged either in the form of numerous empty follicles with or without obvious lumina, or in long, more or less parallel columns. There are often large areas in these nodules in which the parenchyma is replaced partly or wholly by poorly-staining hyaline or granular connective tissue. Sinus-like blood vessels, often of considerable size, may be found in the more degenerate nodules.

Evidence of cellular activity and of hyperplasia in the follicles may be detected in certain of the nodules, or it may be more generalized. The hyperplasia

may be in the form of hummock-like formations in the wall of the follicles in colloid type nodules, consisting of small, and at first empty follicles. The epithelium of the main follicle at the site of the hummock is often columnar in type. In rarer cases the hyperplasia may be of a more widespread nature, and is not unlike those found in certain phases of Graves' disease.

In some specimens there are to be found small cysts containing a papillary development from the lining epithelium, which may fill the whole cyst cavity with a branching structure made up of epithelial cells, often columnar in type, supported on a fine connective-tissue skeleton.

Single nodules and cysts are apparently rare in endemic areas, but among sporadic cases single, well encapsulated nodules and cysts are very common, the remainder of the gland being healthy.

Such tumors have complete capsules, differing in this respect from diffusely nodular goiter, in which imperfect encapsulation of the smaller nodules is the common condition. The appearance of single nodules, both macroscopically and microscopically, does not differ from that of the more obvious nodules met with

in the diffuse variety of the disease.

These single tumors are what are most commonly referred to as thyroid adenomata. They are of two types, colloid and fetal. The colloid adenoma differs in no essential from the large colloid nodules of the diffusely adenomatous goiter.

"Fetal" adenomata are usually single somewhat vascular tumors, often of considerable size, and sometimes grow rapidly, but exhibit little tendency to cystic degeneration, although hyaline changes and central fibrosis are common. These solid cell masses are usually of minute size, but occasionally in goitrous glands can be detected with the naked eye.

The other type of nodule is the Hürthle-cell tumor. It is a rare entity and definitely seems to be a neoplasm. It will not be discussed in the body of the thesis but is here mentioned for the purpose of completeness. The derivation of the tumor tissue is obscure according to Symmers (79). He divides the type into two varieties. One is an adenoma showing no malignant qualities other than pressure effects. The other is a tumor displaying the ability to metastasize, thus a malignant neoplasm. The cut surface of the tumor mass is grayish-red, smooth, and glistening.

Microscopically, it contains large, pale cells arranged in a single layer to form an alveolus. The cytoplasm of these cells is hyaline or finely granular and slightly acidophilic (strongly acidophilic according to Boyd (6)). Intracellular fat-free vacuoles are numerous. The nuclei are small, pale, rather dense, and sometimes finely stippled.

Origin of the Nodule

Since 1883, when Wölfler (88) brought out his "fetal rest" theory, many observers had considered the fetal adenomata positively and the other types of adenoma possibly as arising from original anlagen of thyroid tissue in the gland which failed to disappear and remained as islands of embryonal tissue. On this basis these nodules were considered true tumors.

Since about 1925, most writers have considered Wölfler's idea as of historical value only, while some consider it as a possibility, and only one writer read, Kroger (36), seemed to believe absolutely in it.

The "Hyperplastic-Involutional Theory", as described by Graham (24) (25), is the one most commonly held and explains the origin of the various types of "adenoma" whether they be fetal or colloid in type or of a gradation in between. According to this theory,

the nodulation begins with a localized area of hyperplasia of the thyroid parenchyma which by increasing growth causes an area of atrophy and fibrosis from pressure on and interference with the blood supply to the surrounding tissue. The subsequent replacement fibrosis becomes the capsule of the "adenoma". Kroger (36), Hertzler (29), Brenizer and McKnight (7), and Means (55) seem to hold with the idea advanced by Graham except that they consider the colloid "adenoma" an involutional process and the fetal "adenoma" a neoplasm. They are, in general, vague as to the origin of the fetal adenoma. Hertzler (29) says they are congenital tumors, are not goiters, and are unifluenced by the surrounding thyroid parenchyma. These authors seem to have the opinion that the colloid nodule is an area in which involution from a hyperplastic stage has taken place more rapidly than has been the case in the surrounding tissue. Boyd (6) states that the acini of the hyperinvoluting portion become overdistended with dense colloid. The fibrous septa which normally separate lobules become thickened and a wide zone of fibrous tissue is formed with compression and even obliteration of surrounding acini, producing an intensification of the normal tendency to lobulation well

seen in the fetal thyroid.

According to Graham (25), the primary focus of the nodule consists of a nonencapsulated mass of cells of fairly uniform size and has no orderly or systematic arrangement. Later there is an apparent polarization of cells around empty spaces and the formation of acini. Later, the acini may become distended with colloid. The capsule is formed as described above. The degree of differentiation determines whether the nodule will be fetal in type or colloid or some variation in between or mixed. Graham is merely elucidating upon the theory supported by Wegelin (85), who states that this hyperplasia is a compensatory formation of tissue to replace exhausted tissue in another portion of the gland, thus the predominance of the nodular type of goiter in endemic areas. Rienhoff (72) and Hellwig (28) have their sympathies with the Graham-Wegelin school of thought. Hellwig, on the basis of research conducted both in the United States and Europe, believes that the fetal "adenoma" is the characteristic type of "adenoma" of endemic regions. He points out that the diffuse microfollicular (fetal) goiter occurs in districts of high endemicity, such as the Swiss mountain valleys, whereas it is unknown

in the United States. On the North American continent, which he compares in endemicity to the level countries of Europe, he finds the common structure of goiter to be diffuse colloid or nodular colloid.

That fetal "adenomata" are congenital is the theory advanced by Patterson, et al (64). The presence of fetal characteristics in the adult thyroid is due to failure of maturation caused by extreme hyperactivity and hyperplasia during the development of the gland. This hyperactivity and hyperplasia is brought on by hypothyroidism in the mother. To support this, they point out that in the fetuses of totally thyroidectomized rabbits the thyroid shows definite evidence of a state of extreme hyperactivity. The absorption of thyroxin from the fetus by the mother to make up for her deficit causes a decrease in her blood cholesterol, and produces hypothyroidism in the fetus reflected by a fetal hypercholesteremia. Baumann and Holly (3), in 1926, also found the cholesterol content of the blood of fetuses of partially thyroidectomized and goitrous rabbits to be elevated as much as 100 per cent above normal. To show that this hypercholesteremia is not due to equallization of the high blood cholesterol of the mother across

the placenta, Meigs, et al. (56), proved by means of tagged cholesterol that cholesterol does not pass across the placental barrier.

Nodule or Adenoma?

Eggers (21) defines a neoplasm as a new growth of body tissue, from an unknown mechanism, which reproduces, with more or less fidelity, pre-existing body tissues, and serves no useful purpose in the body. A benign neoplasm is one which is restricted in growth, gains slowly, and does not increase beyond a certain size.

Graham (24) calls the end result of the process of nodulation a neoplasm purely on the basis of morphological characteristics. Warren's (83) classification admits of no other possibility than that thyroid nodules are true tumors. Coller (14) considers the "adenoma" to be a congenital disturbance of the development of the thyroid comparable to the adenofibroma of the mammary gland. Kroger (36), Hertzler (29), Brenizer and McKnight (7), and Means (55), as mentioned before, believe at least the fetal "adenoma" to be neoplastic. Also of the neoplastic school are Crile (17) and Broders (8).

Wegelin (85), who holds a theory in common with

Graham (24) as to the origin of the nodules, differs with him and calls the nodules compensatory growths of thyroid tissue rather than new growths. Under ten per cent of the nodules are neoplastic, according to Boyd (6). These true neoplasms show no evidence of hyperplasia or involution, and are composed of epithelial cells arranged in narrow anastomosing strands. Rienhoff (72) is also of this opinion. Hellwig (28) opposes the neoplastic theory on the basis of geophysiology; Joll (30), on the basis of the pathological picture.

Classification

The classification of goiter is not purely an academic problem, nor is it an easy problem to master. The necessity for identifying the various with the significance that one attaches to the patho-physiology of nodular goiter.

Clinically, the classification as proposed by the Committee on Classification of the American Association for the Study of Goiter (20), and used for teaching purposes during the clinical years at the University of Nebraska College of Medicine, is simple and adequate. Goiter is divided into four types:

Type 1. Nontoxic diffuse goiter
Type 2. Toxic diffuse goiter
Type 3. Nontoxic nodular goiter
Type 4. Toxic nodular goiter

This classification is devoid of the use of the word "adenoma" and thus is more generally acceptable than the equally simple classification proposed by Plummer (51) in 1926. Plummer's classification is as follows with the goiter association's classification in parentheses for the purpose of identification:

A. Endemic goiters
   I. Diffuse colloid (nontoxic smooth goiter)
   II. Adenomatous
      a. with hyperfunction (toxic nodular goiter)
      b. without hyperfunction (nontoxic nodular goiter)
B. Exophthalmic goiter (toxic smooth goiter)

This is a definite improvement over the unwieldy clinical classification as proposed by Moolten (57):

A. Goiters associated with hyperthyroidism
   1. Adolescent goiter
   2. Graves' disease
   3. Adenoma of the thyroid
B. Goiters not associated with hyperthyroidism or associated with hypothyroidism
   1. Adenoma of the thyroid
   2. Colloid
      a. "Burnt out goiter of Crotti"
      b. Simple or endemic goiter
   3. Degenerative forms -- including cystic goiter and malignancy

MacCarty (39) (40) proposed an anatomical classification along with graphic illustrations in 1931 and reiterated its use and practicality in 1940. The

classification that Broders (8) follows at Mayo's is essentially the same with certain minor modifications. The following is MacCarty's classification:

A. (Thyroid Shaped)
- Hypertrophic colloid goiters
- Hypertrophic parenchymatous goiters
- Atrophic parenchymatous goiters

B. (Nodular Shaped)
- Adenomatous goiters without parenchymatous hypertrophy
- Adenomatous goiters with parenchymatous hypertrophy
  - Intra-adenomatous
  - Extra-adenomatous
- Adenomatous goiters with parenchymatous atrophy
  - Intra-adenomatous
  - Extra-adenomatous

In the interests of a uniform nation-wide and world-wide pathological classification of goiter, Hellwig (28) advocates the use of Aschoff's classification. It supposedly covers all general types of goiter found, and its use purportedly would allow the New England pathologist and the middle-western pathologist to talk in the same language and to compare the types of goiter found in their respective localities. This is the Aschoff classification:

A. Diffuse goiter
   1. Congenital diffuse goiter
   2. Diffuse parenchymatous (microfollicular) goiter
   3. Diffuse colloid (macrofollicular) goiter
      a. non-proliferant
      b. proliferant
   4. Exophthalmic goiter

B. Nodular hyperplasia
C. Nodular goiter
   1. Nodular parenchymatous (microfollicular) goiter
   2. Nodular colloid (macrofollicular) goiter
      a. non-proliferant
      b. proliferant
   3. Nodular goiter with extensive epithelial proliferation

Others have tried to classify the tumors of the thyroid. Warren's (83) classification has much in common with most of the classifications:

Benign
   1. Adenoma
      a. embryonal
      b. fetal
      c. simple
         1. Hürthle cell
      d. colloid
   2. Papillary cystadenoma
      a. originating from thyroid
      b. originating from aberrant thyroid
Malignant, etc.

Broders (8) denies the occurence of benign papillomas, papillary adenomas, papillary cystadenomas, and benign metastasizing goiters. He considers them all to be adenocarcinomas. He may well have a point in that Brenizer and McKnight (7) have pointed out the potential malignancy of papillary tumors of the thyroid. Crile's (17) tumors of the lateral aberrant thyroids are practically all papillary adenomas, in which cases there are practically always coexistent tumors in the thyroid gland.

Few American writers report the so-called benign metastasizing adenoma. Kaplan (31) cites two very inconclusive cases of benign metastatic thyroid tissue in which the tumor could not be found in the thyroid gland. The foreign writers (35) (62) (74) report several cases of metastatic adenoma, but American pathologists and clinicians consider such tumors to be malignant. Severance and Johns (76) give six histologic criteria of malignancy:

1. Greater variation in size and shape of tumor cells.
2. Relative increase in mitotic figures; some may be bizarre.
3. Possible presence of tumor cells in definite blood or lymphatic vessels.
4. Hyperchromatism of nuclei.
5. Invasion of capsule by abnormal cells.
6. Invasion of adjacent normal thyroid by abnormal cells

Portmann (69) reports that the Cleveland Clinic uses Graham's criteria of malignancy:

1. Invasion of blood vessels with formation of thrombi or polyps of neoplastic cells.
2. Structure of these is similar to the parent tumor.

Clinical Picture

When nodular goiter is non-toxic, its crimes are much the same as those of the smooth non-toxic goiter, namely obstruction causing suffocation or dysphagia and unsightliness. The degenerative changes that are

prone to occur in nodular goiter will be discussed later.

When a nodular goiter becomes toxic, the picture becomes confused. Is "toxic adenoma" the same condition as exophthalmic goiter? In scanning the textbooks used in the college of medicine, I find no unanimity of opinion as to the nature of toxic nodular goiter. DuBois (20), writing in Cecil's medicine text, finds no essential difference between exophthalmic goiter and toxic adenoma, and considers them to be clinical manifestations of the same disease. Christian (12) takes an opposite stand. In Christopher's Textbook of Surgery, Pemberton and Haines (65) write that toxic adenoma is a distinct entity, and cite cases where enucleation of a single adenoma caused cessation of hyperthyroidism and where hyperthyroidism occured in a person who had previously had myxedema -- the thyroid tissue was markedly atrophic, but contained numerous adenomas. Boyd (6) sees no reason to suppose that the "adenoma" is in the slightest degree responsible for the symptoms of thyrotoxicosis.

There is reason for this confusion as there usually is a difference in the clinical picture presented by toxic smooth and toxic nodular goiter. Joll (30)

skirts the problem nicely by giving lip service to the unitarian school of thought and then setting up two clinical types of goiter. One is primary thyrotoxicosis which he defines as thyrotoxicosis affecting a previously healthy gland and producing symptoms by the elaboration of a perverted secretion in combination with an excess of normal secretion. The other is secondary thyrotoxicosis in which toxic symptoms are engrafted on a pre-existent goiter. His differentiation of the two diseases is much the same as is taught in the standard textbooks and medical lectures. He has arranged the symptoms in a convenient form for comparison. The following is an exact reproduction:

Primary Toxic Goitre	Secondary Toxic Goitre
Onset may be acute and is often rapid.	Onset generally very insidious. Acute forms very rare, and almost exclusively due to excessive iodine medication.
Young adults, usually previously goitre-free, affected.	Middle-aged patients, often goitr-bearers of long standing, affected.
Exophthalmos common and often severe.	Exophthalmos rare and usually slight.
Nervous phenomena may be very prominent and often dominate the case.	Nervous phenomena are slight or absent.
Myocardial and vascular lesions may be inconspic-	Myocardial and vascular degeneration are usually

Primary Toxic Goitre	Secondary Toxic Goitre
uous until the later stages.	prominent and early features.
Gastro-intestinal and other crises not uncommon.	Crises very rare.
Metabolic disorders are common. B.M.R. may be higher than + 100 per cent.	Metabolic disorders less common. B.M.R. rarely reaches + 50 per cent.
Goitre usually diffuse, hyperplastic, and symmetrical, rarely very large.	Goitre nodular, and may be enormous. Exceptionally, goitre may be diffuse and parenchymatous or colloid in type.
Secondary anemias rare.	Secondary anemias not uncommon.
Iodine medication often dramatic in its effect in reducing activity of symptoms.	Iodine medication, though often beneficial, not so striking in effect.
May rapidly progress to a fatal termination in delirium and coma.	The disease is a chronic one, and death, when due to thyrotoxicosis, is the result of myocardial and vascular lesions.
Operation risks appreciable.	Operation risks less than in primary group.
Operation cures about 90 per cent.	Operation cures approach 100 per cent.
Recurrences 6.5 per cent.	Recurrences 0.1 per cent.

Plummer (51), the foremost exponent of the theory of "toxic adenoma", explains the symptoms of toxic

adenomatous goiter purely on the basis of an excess of the normal secretion of the thyroid and states that the phenomena occuring in the disease in no way differ from those following the administration of dessicated thyroid or thyroxin. He postulates that the symptoms of exophthalmic goiter are due to an abnormal product of the thyroid, possibly an incompletely iodized thyroxin. He believes that adenomatous tissue has an inherent tendency to hyperfunction. Essential hypertension, pregnancy, and pituitary disease favor the development of adenoma and may excite it to hyperfunction, increasing the rate of exhaustion of thyroxin with a resultant increase in the intensity of stimulation of thyroid. The same writer (66) reports a higher incidence of both exophthalmic goiter and adenomatous goiter with hyperthyroidism between 1924 and 1931. He referred to this as an epidemic. The onset of the "epidemic" was almost if not coincident with the introduction of iodized salt -- but evidence was insufficient to incriminate it. The relative and total amounts of thyroxin and abnormal agent delivered are determined by an equation in which the degree of stimulation, available iodine, and training of the gland are important factors. Training of the gland refers to how much

thyroxin the gland will turn out under optimal conditions. Haines (26) and Broders (8) (9), also Mayo men agree with Plummer. Broders (9) takes the extreme view by writing, "When one sees an adenoma in which columnar epithelium is prominent, it is safe to consider it a toxic adenoma." He also restricts "toxic adenoma" to those in which the columnar epithelium is limited to the adenoma. Also with the Mayo school of thought are Severance and Johns (76), Nienstedt (59), Hertzler (29), and Clute and Albright (13).

Means (55) doubts the existence of such an entity as "toxic adenoma", but nevertheless includes it in his classification of toxic goiters. Graham (25) takes an extremely negative viewpoint on the whole topic of hyperplasia and hypertrophy whether it occurs in a nodular or smooth goiter, and considers hyperthyroidism to be the same condition in both types of enlargement. He makes the following rather belligerent assertion: "there is certainly no legitimate excuse for fostering the fallacy that hypertrophy and hyperplasia are characteristic or specific for hyperthyroidism. . ."

That a specific habitus is prone or almost doomed to toxic goiter was the view advanced by Warthin (84)

in 1929 and supported later by Simpson (77). These individuals are of the "thymicolymphatic diathesis" which is essentially an asthenic type. In addition they found that patients with "toxic adenoma" or Graves' disease had hyperplastic lymphoid tissue in the thyroid; enlarged thymus; lymphoid tissue hyperplasia of the spleen, lymph nodes, Peyer's patches, and solitary lymph follicles of the intestines; hypoplasia, chiefly medullary, of adrenals and hypoplasia of the heart and blood vessels. Summed up, the disturbance in the morphology and function of the thyroid gland is but one manifestation of an abnormality involving many other structures.

In an endeavor to establish an index for classifying nodular goiters as to activity, Abel (1) measured the height of acinar cells in normal thyroids, toxic nodular goiters, non-toxic nodular goiters, and toxic diffuse goiters. In plotting the height of cells against their frequency in blocks of one hundred cells, he found the curves for the toxic goiters to be almost identical. The non-toxic nodular goiter took up a place somewhat intermediate between the normal curve and the toxic curve, but was too close to the latter to be of practical use.

Hellwig (28) believes that both toxic nodular and exophthalmic goiter develop on the basis of macrofollicular colloid goiter.

Puppel and Curtis (18) (19) (70) in a series of studies on the excretion of iodine in the urine, feces, and sweat of goitrous patients found patients with toxic nodular goiter to have a greater increase in urinary excretion of iodine than patients with exophthalmic goiter. The blood iodine and basal metabolic rate were increased less than in exophthalmic goiter. In nontoxic nodular goiter, urinary excretion of iodine, blood iodine, and B.M.R. are normal or may be slightly sub-normal. The total excretion of iodine in both types of toxic goiter was practically the same; there was a difference, however, in the relative amounts of iodine excreted in the urine and feces. Post-operatively both types of goiter showed a return to normal in B.M.R., blood iodine, iodine excretion, and iodine balance, indicating that increased excretion of iodine in toxic goiter results directly or indirectly from an overfunctioning gland.

In trying to differentiate between "toxic adenoma" and exophthalmic goiter on the basis of response to iodine therapy, Coller and Potter (15) found that when

iodine is administered to "toxic adenomas" the declivity of the B.M.R. curves is less than in exophthalmic goiter and the curves do not show a uniform downward trend. Forty-six per cent of the toxic nodular goiters were not affected favorably by iodine therapy, and one of the main characteristics of the whole toxic nodular series was a lack of uniformity of reaction. Eight per cent were made worse by iodine. They concluded that one can not prophesy what effect iodine will have on adenomatous goiter, but recommended its use in the pre-operative treatment of all types of toxic goiter. They believe that iodine has no part in the non-operative treatment of nodular goiter. According to their study, exophthalmic goiter and adenomatous goiter can not proved to be similar entities on the basis of reactions to iodine. There are several theories as to the action of iodine in toxic goiter. Plummer and Boothby (67) believe that exophthalmic goiter is a dysthyroidism that is converted into a pure hyperthyroidism by iodine. Marine's (44) theory is that iodine produces a response in the thyroid in which there is a rapid distention of the alveoli with colloid, causing a pressure retention with temporary blocking of excretion which is soon compensated for by

a return of symptoms. The Thompsons and Means (80) (81) have conducted studies on the response of exophthalmic goiter in a non-goitrous area (Boston) with that seen in a goitrous area (Chicago). They concluded that the response is the same in both areas except that it is a little slower in the goitrous regions. All other characteristics of the disease were essentially the same.

Keveno (71) reported that adenomatous goiters with toxic symptoms responded to thiouracil in certain cases. Where they did, the glands and adenomas were larger and softer than in the beginning.

Although nodular goiter is usually first noticed during or shortly after puberty, Kennedy (34) reviewed sixty-two cases of nodular goiter found in children between the ages of four and fourteen. Slightly less than eighty per cent were "adenomas", twenty per cent were carcinomas, and there were two cases of thyroiditis. In no case of nodular goiter was there evidence of hyperactivity of the gland. In his experience hyperthyroidism in childhood occurs only with exophthalmic goiter. Stevens and Waite (78) wrote of a case in which a mass in the thyroid of a girl of seven years was removed and found to be adenocarcinoma. The nodule

had been present since birth and had not changed in size; there were no toxic symptoms, but there was some dysphonia and huskiness. The histological appearance of the tumor was such that they believed that malignant change was a recent occurence.

Most of the writers who touched on the subject pointed out the definite chance of malignant change in nodular goiter, especially in ones in which there is but a single nodule; but Graham (25) believes that the danger of carcinoma is much overrated. Lahey (37) believes that most cancers of the thyroid originate in a lesion which is primarily benign, that is the discrete fetal or embryonal adenoma. He recommends removal of all discrete adenomas regardless of their size and regardless of the age of patient. He gives as gross indications of malignant change, a change in the consistency of the tumor, a loss of discrete outline of the tumor, a loss of mobility in a previously mobile tumor, and paralysis of the recurrent laryngeal nerve on the same side as the tumor. If a careful search were made, it is the opinion of Goetsch (22) that nearly 100 per cent of the carcinomas of the thyroid would be found to originate from fetal adenomata. The few cases of carcinoma arising in exophthalmic goiter which have

been reported probably could have been shown to arise from minute fetal adenomata, according to his belief. Coller (14) reports that 98.8 per cent of cancers of the thyroid show evidence of pre-existing goiter, but believes that only eighty per cent of these goiters were adenomatous. Warren (83) believes that an isolated nodule in the thyroid has a ten times greater chance of being malignant than any other type of thyroid enlargement. Wegelin (85) points out that the highest incidence of malignancy of the thyroid is found in the endemic areas. In Switzerland, carcinoma of the thyroid is as common as carcinoma of the skin; and if the mesothelial malignancies of the thyroid were included, the incidence would exceed that of malignancy of the skin. He attaches a goitrous origin to practically all cancerous growths of the gland, excluding only teratomas and papillary cystadenomas. A fair number of sarcomas arise from the capsule of the adenoma; often the adenomatous tissue is so prominent that they are called colloid-adenosarcomas. Hemangioendotheliomas arise chiefly from old hemorrhagic adenomatous nodules. Carcinosarcomas often arise from long-standing goiter. The highest incidence of expected carcinoma developing in nodular

goiter is postulated by Clute and Albright (13) at five or six per cent. This is on the basis that ten per cent of the adenomatous goiters that they see show malignant degeneration, but that a fair share of people with adenomatous goiter never seek medical attention. The lowest expected incidence of carcinoma in adenomatous goiter is predicted by Binkley (5), who expects only 2.5 per cent of them to become malignant. Mayo (52) ranks just above him, prophesying malignant degeneration in three per cent.

Pressure effects created by the nodular goiter within the thyroid gland may bring on a myxedematous condition by compression of the normal throid parenchyma. When the adenomatous tissue hyperfunctions, as reported by Haines and Pemberton (65) and Kroger (36), a very bizarre picture may result combining features of hypo- and hyperthyroidism.

The various types of degeneration that are prone to occur in nodular goiter have already been mentioned in the section on pathology, however, the effects produced in the organism have not been discussed. Plummer and Broders (68) have described a condition which they call acute capsulitis, occuring in the capsule of a cystic degenerated or partially degenerated adenoma.

The symptoms are sudden swelling of the gland, accompanied by local pain, tenderness, and inflammation. The condition must be differentiated from gross intra-adenomatous hemorrhage -- itself another degenerative change.

Several authorities have described variations on what Hertzler (29) named the "degenerated goiter syndrome". Typically, the following picture is presented: a hitherto unknown goiter degenerates producing weakness, dyspnea on exertion, palpitation, loss of weight, increased heart rate, and possibly a cardiac irregularity. It usually occurs in nodular goiter. Chesky (11), of the Hertzler Clinic, reported fifteen cases of long-standing nodular goiter in which eight of the patients had auricular fibrillation. All of these goiters showed degenerative changes, and in some the acini had completely disappeared in the center, being replaced by fibrous tissue. The least degeneration was shown around the periphery of the gland, but here these epithelial cells were of the low type showing regressive rather than hyperfunctioning activity. Wetherell (86) also has noticed this clinical syndrome in New York, and also attributes the manifestations to an abnormal secretion elaborated by a degenerating thyroid nodule.

A common finding is a B.M.R. between plus fifteen and minus twenty.

Premature ageing in patients who are subject to cystic degeneration of the thyroid has been observed by McGregor (54). This occurs especially when the cyst replaces a pre-existing fetal adenoma, and is due presumably to absorption of the cyst contents into the general circulation producing toxic symptoms entirely different from those caused by hyperthyroidism. Quantitative chemical analysis of the cyst reveals the presence of cholesterol in relatively large quantities. As would be expected, the condition occurs more often in women. The patient looks tired; appears ten or fifteen years older than the stated age; the skin is dry, wrinkled, and lifeless in appearance; the hair is turning gray prematurely, and the nails chip. There are none of the symptoms associated with thyrotoxicosis. Almost all of the symptoms disappear after enucleation of the cyst and the incidence of recurrence is no greater than one would expect in an individual who had never had any dysfunction of the gland.

The general considerations considered by surgeons who recommend the removal of all thyroid adenomata, especially of the discrete variety, is summed up by

Haines (26). He recommends their removal to prevent possible development of carcinoma, to prevent pressure on the trachea, and to prevent the development of hyperthyroidism. Most of the authorities, including Lahey (37), who believe that a single nodule can be incriminated in thyrotoxicosis, also consider enucleation of the nodule to be a sufficiently extensive operation. Brenizer and McKnight (7), however, believe that some surrounding tissue should be removed with the nodule in case the growth is found to be malignant.

CONCLUSIONS

In analyzing the opinions of the experts concerning the nature of nodular goiter, I could find no correlation between the views expressed and the geographic area in which the writer was located. In general, the Mayo group hold a common theory, namely that toxic nodular goiter is a distinct clinical entity. Also in general, the New England group line up in opposition to the Mayo group. However, the exceptions are such that predictions as to the opinion of a given writer based purely upon the geographic location of his clinic would be extremely hazardous.

The primary cause of simple or endemic and of the fetal and colloid types of nodular goiter is inadequate supply or lack of iodine. Inadequate supply of iodine is a relative term. The amount of iodine needed by the thyroid to supply sufficient hormone and still retain its structural integrity is variable from gland to gland, and in the same gland at different ages and conditions of stress. The ages at which simple goiter most frequently develops are during fetal life, during pregnancy and lactation, during puberty, and during the menopause. In the United States nodular goiter does

not appear until after puberty. The basis of this finding is probably the longer period taken for the development of the nodules, in contrast to the fairly common occurence of nodular goiter in the severe endemic areas of Europe. A point that should be emphasized is the ability of the given thyroid to elaborate hormone. Those who postulate other causes of goiter than inadequate supply of iodine set up conditions which not inconceivably could so alter the thyroid parenchyma that it is unable to utilize iodine no matter how much of the element is supplied. This constitutional make-up or "training" is probably in the main hereditary, but capable of being modified by environmental factors.

Nodular goiter, per se, should not be considered as neoplastic. One of the conditions that must be satisfied for a growth to be neoplastic is that the mechanism of origin be unknown. Since I believe that most nodular goiters arise in response to inadequacy of iodine supply, and as a corollary from hypertrophy in one portion of the gland in compensation for exhaustion of another portion of the gland, it would seem inconsistent to consider the growths neoplastic. Nodules in the thyroid which on histological examination

show epithelial cells in narrow anastomosing threads seem to have a much better case for being neoplasms inasmuch as no cycle for their development has been observed. These may be considered true adenomata. The status of papillomas and papillary cystadenomas is in dispute as to whether they are benign or malignant growths. It would seem a politic move to consider them benign until proven malignant. The criteria for malignancy of the thyroid are essentially the same as for tumors in other organs of the body. However, special emphasis should be placed upon invasion of blood vessels with the formation of thrombi or polyps of neoplastic cells.

It would seem logical to conclude that thyrotoxicosis is the same condition whether it occurs in nodular or smooth goiter. Many of the symptoms previously ascribed to a difference in the type of pathology might just as well be explained on the basis of the age of the patient. Large doses of dessicated thyroid or thyroxin cause in the normal individual tachycardia, increased nervousness, and various other phenomena cited in the body of the thesis. In younger persons might not the predominance of nervous symptoms be explained on the basis of the natural lability of the nervous

system of that age group? Following the same line of reasoning, in the older age group affected by toxic nodular goiter might not the auricular fibrillation and cardiac decompensation be the result of too much stress put on an already degenerating myocardium by the excess of thyroid hormone.

The response to iodine seems to be of little value in differentiating between toxic nodular and toxic smooth goiter. Possibly some of the inconsistent results from treatment of toxic nodular goiter with iodine have resulted from poor circulation in the gland occasioned by barriers in the form of fibrous tissue capsules around the nodules. The inciting of toxicity in the nodular goiter by the use of iodine (so-called Iod-Basedow or Jod-Basedow) is of no clinical significance. Iodine should be used pre-operatively in toxic nodular goiter.

For clinical purposes the classification of the American Association for the Study of Goiter should be used, namely:

Type 1. Nontoxic diffuse goiter
Type 2. Toxic diffuse goiter
Type 3. Nontoxic nodular goiter
Type 4. Toxic nodular goiter

This is advocated both for the purpose of uniformity

of nomenclature and to prevent the loose usage of the term "adenoma" which should be reserved for the benign neoplasms. The diagnosis of neoplasm of the thyroid, with the occasional exception of carcinoma, cannot be made clinically. Thus "adenoma of the thyroid" should be barred from the clinician's vocabulary except as a speculative diagnosis, and reserved almost exclusively for the use of the pathologist.

Theoretically, the Aschoff classification of thyroid diseases as advocated by Hellwig, if adopted universally by the pathologists, would provide a more precise basis for the comparison of goiter in different regions of America and of the world. Such a comparison might immensely clarify the somewhat cloudy picture of thyroid disease.

Nodular goiter, apart from its possible participation in thyrotoxicosis, has certain inherent dangers. This is especially true of the single discrete nodule. The dangers of nodular goiter lie in its susceptibility to degeneration. That absorption of toxic products from degeneration cysts in the thyroid may take place and produce a generalized systemic reaction is no more untenable than the belief in absorption of toxins from infected foci or tumors anywhere in the body. Malignant

degeneration of thyroid nodules is an ever present danger, but its occurence fortunately is not too common.

Enucleation of thyroid nodules without resection of a portion of the gland seems to have no clinical indication. This applies especially to cases of toxic nodular goiter as I can see no possible way to determine clinically that the toxic symptoms are being produced exclusively by hyperfunction of the nodule and that the thyroid parenchyma is taking no part. In view of the possibility of the presence of malignant change in a nodule, it would seem to be poor surgical judgment not to remove a portion of the seemingly normal surrounding tissue along with the nodule in operations in which subtotal thyroidectomy is not necessarily indicated -- eg., an operation for cosmetic purposes.

The surgical handling of a toxic goiter should be the same whether it be smooth or nodular. The strictly medical treatment of toxic nodular goiter seems ill-advised.

SUMMARY

1. The history of our knowledge of the thyroid gland has been reviewed with special emphasis on our knowledge of goiter.

2. The thyroid gland, as a whole, has been discussed with descriptions of its normal development, anatomy, histology, physiology and chemistry, and action of its hormone.

3. The problem of simple or endemic goiter has been reviewed with the presentation of the various theories as to its mode of origin.

4. Nodular goiter has been discussed from the viewpoint of etiology, pathology, classification, and clinical picture.

5. Conclusions have been drawn as to the nature of nodular goiter:

   a. Nodules of the fetal, colloid, and intermediate types arise from the same cause as do endemic goiter, namely inadequate iodine or inadequacy of the gland to utilize the iodine available.

   b. Most nodular goiter is not neoplastic in nature.

   c. Thyrotoxicosis is the same condition whether occuring in smooth or nodular goiter.

   d. The classification as recommended by the American Association for the Study of Goiter is best suited for clinical use.

   e. The Aschoff classification is recommended to the pathologists.

   f. Nodular goiter has certain inherent dangers by virtue of its susceptibility to degeneration, namely absorption of products of degeneration and malignancy.

g. Enucleation of the thyroid nodule without resection and the strictly medical treatment of toxic nodular goiter is not recommended.

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