in the form of miliary tubercles or in that of caseous tuberculous foci, have been noted.

The thymus is the seat of various kinds of tumors, and is the starting-point of a considerable number of the neoplasms located in the anterior mediastinum. Various teratomas have been found in connection with it, the most common one being a dermoid cyst with hair, epithelium, and fatty contents similar to the dermoids of the ovary. A more frequent variety of thymic tumor is one taking a lymphoid structure and designated lymphoma or lymphosarcoma, depending on its extent and the production of metastases. However, since the lymphatic glands in the anterior mediastinum and about the bronchi may also become the seat of these tumors, it often becomes difficult to decide whether the thymus has been primarily or secondarily affected. The question may at times be determined histologically by the discovery of Hassall's corpuscles in the primary tumor. Besides the small-celled lymphosarcoma, other varieties of sarcoma may occur, and carcinoma, presumably originating from the remaining foci of epithelial tissue, is occasionally encountered.

Extensive lymphoid infiltration and enlargement of the thymus may attend leukæmia and pseudoleukæmia.

Peculiar cysts of the thymus, probably at one time misunderstood and consequently designated Dubois's abscesses, have been carefully studied by Chiari, who regards them as originating from a growth of thymic tissue into the corpuscles of Hassall. Besides these spurious abscesses there are cavities with softened contents, properly called Dubois's abscesses, due to the softening of syphilitic nodules (small gummas). Syphilitic infection of the thymus may also manifest itself by a hyperplasia of the organ, or by a diffuse connective-tissue overgrowth with consequent induration. *A. P. Ohlmacher.*

LITERATURE.

As has already been mentioned, much of the literature upon the thymus, especially as to its hypertrophy and hyperplasia, should properly be classed with that bearing upon status lymphaticus. A particularly valuable paper giving the historical references is Ducrot's thesis ("De la Mort subite chez les jeunes enfants par hypertrophie du thymus au point de vue médico-légal," Paris, 1901). A more extensive work dealing with the thymus as a whole is Friedleben's monograph ("Die Physiologie der Thymusdrüse in Gesundheit und Krankheit," 1858). A thorough summary of the more recent literature is to be found in Klein's review ("Neuere Arbeiten über die Glandula thymus," *Cent. f. allgemeine Pathologie*, Bd. ix., Nos. 16, 17, 1898). From these three sources the student can obtain a reference to most of the literature dealing with the thymus except as pertains to certain special aspects of the embryology, anatomy, and histology, for which the standard text-books may be consulted.

THYROID.—ANATOMY.—There are few organs in the body that show normally so many and so great variations in structure, both gross and minute, as the thyroid. This is to be explained by the fact that it has its origin in three independent embryonal structures, so that in their fusion there are many opportunities for variations. Again, the absence of any excretory duct probably permits of wider variations than might otherwise occur, for no matter how arranged or where located the gland can accomplish its entire function, provided only that it has proper circulation. Ordinarily it presents two lateral lobes connected by an isthmus, which latter lies across the trachea from the second to the fourth tracheal rings, inclusive. This isthmus is absent in from ten to fifteen per cent. of individuals. When present, it may merely consist of a mass of fibrous tissue containing a minimum of gland tissue, or it may form the largest of the three lobes, with all possible intervening variations. Quite rarely, *i.e.*, in about one per cent., the isthmus exists as an independent lobe. When the isthmus is absent the lateral lobes are often so closely applied that the absence of the isthmus may be completely overlooked. At the level of the isthmus, the recurrent laryngeal nerve lies in the angle between the œsophagus and the trachea, being covered externally by the lateral lobe on each side. In front, the gland is covered by the sterno-hyoid, the sterno-thyroid, and the omo-hyoid muscles. Laterally, the lobes extend outward in front of the common carotid arteries. The lower end of each lateral lobe is usually at the fifth or sixth ring of the trachea, and the upper end is at the middle of the thyroid cartilage. The lower edge is embedded in a mass of fatty connective tissue, which is of some surgical importance, since it passes without any demarcation into the anterior mediastinum. Behind, it is attached by tough fibrous tissue to the larynx and trachea, so that it moves with them in swallowing. When the head is thrown back, the distance of 2 mm. that lies between the lower border and the sternal notch is doubled (Sappey).

Frequently a conical process, called the "pyramid of Lalouette," extends upward to be attached to the hyoid bone, thyroid cartilage, or thyro-hyoid membrane. This may arise from the isthmus or from either or both lateral lobes, its shape and size also presenting wide variations. Its frequency varies greatly according to different observers. Marshall found it in 26 out of 60 thyroids, or 43 per cent.; Streckeisen in 104 out of 153; Zoja in 109 out of 147, or 74 per cent.; while the writer found it with 36 of 60 thyroids, or 60 per cent. In 10 of these last it arose from the right lobe, in 12 from the left, in 8 from the isthmus, in 5 from both lobes, and in 1 from the left lobe and from the isthmus. In 21 it was attached to the thyroid cartilage or thyro-hyoid membrane, and to the hyoid bone in 15. In one instance the pyramid was split up into a chain of isolated masses of gland tissue, which would have to be classified as accessory thyroids. In structure the pyramid generally consists of regular gland tissue near its base, but the colloid material disappears as it ascends, and the vesicles become mere groups of epithelial cells, which are gradually replaced by fibrous and muscular tissue, until near the upper part of the pyramid they disappear entirely. If the muscle fibres are numerous the upper part is considered a separate muscle, and called the *levator glandulæ thyroideæ*. The pyramids are considered by Bland Sutton to represent part of the original thyroglossal duct.

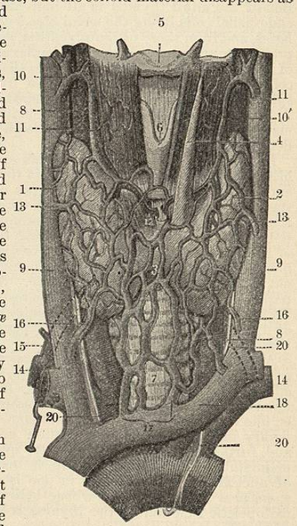

FIG. 4711.—The Thyroid Gland and its Relations. (Testut.) 1, Right lobe; 2, left lobe; 3, isthmus; 4, pyramid of Lalouette; 5, hyoid bone; 6, thyroid cartilage; 7, trachea; 8, carotid artery; 9, internal jugular vein; 10′, superior thyroid vein; 10, thyro-lingual-fascial vein; 11, superior thyroid artery; 12, inferior laryngeal vessels; 13, median thyroid vein; 14, subclavian artery; 15, inferior thyroid artery; 16, lateral inferior thyroid veins; 17, median inferior thyroid veins; 18, left brachiocephalic vein; 19, arch of the aorta; 20, pneumogastric nerve.

In proportion to its weight the thyroid has perhaps the largest blood supply of any organ of the body, the blood reaching it through the superior and inferior thyroid arteries on each side, and occasionally from the thyroidea ima. Following the trabeculæ these vessels break up into a rich meshwork of capillaries about the vesicles. In some places these capillaries even penetrate the basement membrane and come into direct contact with the

secreting cells. So great is the vascularity, that when an active dilatation of its vessels occurs the gland increases noticeably in size, and in this condition a distinct pulsation can be felt throughout the gland. The veins unite to form the superior, middle, and inferior thyroid veins, the two former of which empty into the internal jugular vein, the last into the innominate. They are devoid of valves, and a rich plexus surrounds the gland, often causing much bleeding in operations. Some authors have described collections of a colloid-like substance in the veins of the gland, and suggested that this was the method by which the gland disposed of its secretion, *i.e.*, directly into the circulation. However, these appearances are probably due to accidental extravasations occurring in the handling of the gland. It seems most probable that the excretion of the colloid substance occurs through the lymph channels, which are very numerous in the thyroid and lie in direct contact with the basement membrane of the vesicles, sometimes even with the gland cells themselves. In their lumen colloid is usually to be found, distinguished from other substances by its staining with Van Gieson's stain. After free anastomosis the lymph vessels leave the gland and pass through the superior and inferior deep cervical glands. (See description of lymphatics under "Tumors of the Thyroid.")

The nerves of the thyroid come from the middle and inferior cervical sympathetic ganglia, and pass into it with the blood-vessels. The recurrent and external laryngeal, the hypoglossal, and the vagus all send filaments to the gland, but these all seem to be vaso-motor or secretory, that is to say, they are all of sympathetic origin (Kölliker). The branches run to the bases of the epithelial cells, but the actual endings are not exactly determined.

The weight of the thyroid seems to vary greatly in different countries, since most German authors (Virchow, Rauber) place it at from 30 to 60 gm.; Schaefer in England gives it as 30–40 gm.; Poirier and Charpy in France give the average as 22–24 gm. In sixty thyroids removed in this country, I found the average weight but 22 gm. It would seem that in goitrous countries the normal gland is larger than in non-goitrous countries. The thyroid shows the effects of senility sooner and more than any other organ that is not essentially reproductive. In my series in persons over forty-five years of age the average weight was but 16 gm., while in people between twenty and forty-five years it averaged 25 gm. Differing from the other organs, it is larger, as a rule, in women than in men—a fact which, together with its early atrophy, indicates its close relation to the reproductive organs. It is relatively larger in infants than in adults; in the former the proportion to the body weight being 1 to 700 or 1,000, in the latter 1 to 1,500 or 2,200. According to Huschke there is even a decrease in size after birth, followed by a rapid growth at puberty. In the adult the transverse measurement is usually 50–60 mm., antero-posterior thickness of the lateral lobes 18–20 mm., of the isthmus 6–8 mm.; length of the lateral lobes 50 mm.; height of the isthmus, 5–15 mm. The right lobe is slightly larger when a considerable number of cases is averaged, although often in individual glands the opposite is true.

DEVELOPMENT.—Three separate "anlagen" unite to form the human thyroid. 1. A median diverticulum of the pharyngeal hypoblast pushes its way downward, and forms a tube that is connected with the base of the tongue. Subsequently it becomes solid, its upper end forming the foramen cæcum, from its lower end developing the isthmus, part of the lateral lobes, the pyramids (when they are present), and occasionally accessory thyroids. It sometimes happens that this structure remains in the adult as the "*ductus lingualis.*" 2. From the fourth visceral cleft on each side spring pouches which pass in front of the larynx and unite with the lower end of the median diverticulum, ultimately forming the outer part of the lateral lobes. These three masses fuse to form a horseshoe-shaped structure encircling the embryonic larynx, and are separated from their origin in the hypoblast. At first the gland consists merely of rod-like columns of epithelial cells, resulting from the division and branching of its original rudiments. The ingrowing connective tissue divides these cords of cells into short

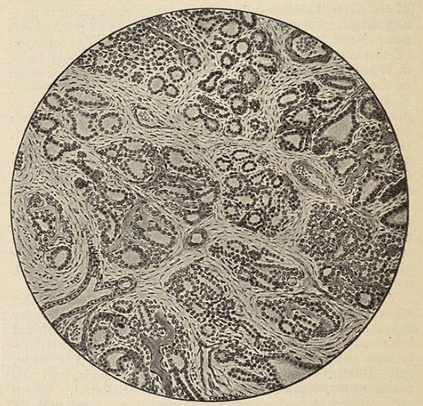

FIG. 4712.—Thyroid of Fœtus at Term. The lobular outlines are more prominent than in the adult; there is no colloid in the acini.

segments, which form the vesicles later, when colloid is secreted. Colloid formation begins in intra-uterine life, but the vesicles are not generally filled until some time after birth, section of the gland of a new-born child showing but few of the acini containing colloid. Because of the method of formation, in the fœtus a lobular structure is distinct, but in the adult this is generally absent or indistinct.

HISTOLOGY.—Fully as great variations are seen microscopically in the thyroids of persons who die of diseases that have no known effect on the thyroid, as have been noted in the gross anatomy. Study of the thyroids from consecutive autopsies shows such a variety of conditions as to suggest that perhaps this organ suffers much more in disease than we have reason to suspect from any clinical evidences. What may be considered the normal structure is described most briefly by saying that it differs from other tubular glands chiefly in having the tubules closed and filled with colloid to varying degrees of distention. The arrangement of capsule, septa, basement membrane, vessels, and nerves is that common to glandular organs in general. By reconstruction methods Streiff has shown that the vesicles are not always spherical sacs, but often are tubular, and frequently are sacculated. The size of the vesicles varies greatly, some being quite without lumen, while others are more than half a millimetre in diameter. As the epithelial cells are modified by the pressure of the colloid in the lumen of the acinus, they vary much in size and shape from those that are distinctly columnar in empty acini to those flattened, in distended sacs, to the nature of an endothelial cell. For the most part they are cuboidal, with a small spherical nucleus that stains more intensely than that of most epithelial cells. They are described as of two kinds—the chief cells and the colloid cells. The chief cells, which form by far the greater part, are clear or with very fine granules and have no distinct membrane, but seem to blend with one another, their outer ends resting on the basement membrane, the inner lying in the colloid substance. The colloid cells are characterized by a more granular and opaque appearance, obscuring the nucleus, and they are lower than the chief cells, from which they seem to be derived. The granules stain like colloid, and

they seem to become converted into this substance, to be replaced by new cells from the chief cells. All stages between these forms may be found. Acidophile granules are also described, which are considered analogous to the zymogen granules of other glands. The colloid content of the alveoli stains a clear pink-white eosin, and is usually structureless. Often, however, nuclei or entire cells are present, but the frequently observed total exfoliation of the epithelial cells into the colloid is probably to be interpreted as a post-mortem occurrence, quite the same as the desquamation of the endothelium of blood-vessels. Red corpuscles are frequently found, apparently normally, and it is stated that they will retain their form and staining properties for a very long time in the colloid. However, pigment from this source is frequently present. The vacuoles that often fringe the colloid are probably for the most part, if not entirely, the result of shrinkage in the hardening process. Ernest considers the orange, or yellowish-brown color assumed by the colloid when stained by Van Gieson's method to be characteristic, but this is by no means constant; sometimes it gives a good red color. Fat is constantly found in the epithelial cells of the thyroid as well as the parathyroids and hypophysis, increasing in amount with age (Erdheim).

The stroma of the gland is scanty in the adult, but more abundant both in infancy and in old age. Larger septa of very dense fibrous tissue separate the original lobules of the gland, while bands that are often extremely thin separate individual acini. In it are the wide, colloid-filled lymphatics, the abundant vessels, and the nerve fibres, which are mostly non-medullated. There are no intrathyroid ganglia, but simple ganglion cells of very irregular form, which, as a matter of fact, are not fully distinguished from branched connective-tissue corpuscles (Poirier and Charpy). Between the follicles are often found groups of cells that seem to indicate undeveloped follicles, even to the extent of sometimes containing colloid droplets. What are considered to be embryonal rests are found, especially under the capsule.

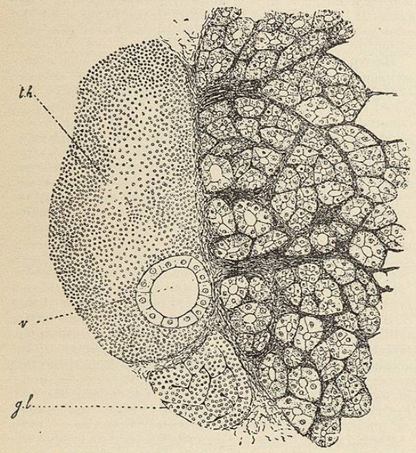

FIG. 4713.—Parathyroid, Thymic Vesicle, and Thymic Lobule of New-Born Guinea-pig. (Poirier and Charpy.) *th.* External thymic lobule; *v.* thymic vesicle; *g.l.* external parathyroid.

The cells lie with little order in the stroma, and have large, chromatin-rich nuclei and little cytoplasm. Their exact nature is not settled. Bozzi found no alterations in embryonal rests present in small stumps of gland tissue remaining after removing the greater part of the gland, nor did their presence prevent the death of the animal, suggesting that perhaps they are not really embryonal rests.

Parathyroids.—These organs are composed of columns of epithelial cells, with large, deeply staining nuclei, and a rather small amount of cytoplasm. They resemble the carotid glands in structure, but the thyroid not at all, and it is considered by Prenant that they are derived from the fourth inner branchial cleft, from which the thymus and the lateral rudiments of the thyroid are also derived. Gley believed that they represented embryonic rudiments of the thyroid, but, as will be shown later under Physiology, this interpretation is not correct. For further description of these organs see under *Goitre*, Vol. IV., p. 378, and under *Parathyroid*, Vol. VI., p. 506.

Thymic Lobules.—As a rule these little-known bodies are four in number, but sometimes there are but two, and in some animals they are lacking (Nicolas). There are two external lobules, usually on the posterior surface of the lateral lobe; and two internal lobules, in the centre of the lateral lobes, surrounded on all sides by glandular tissue, or sometimes they are near the tracheal face. They possess the structure of the thymus, even to the concentric epithelial corpuscles, but they are often mistaken for lymph nodules. They are ascribed to the common origin of the lateral lobes of the thymus and thyroid in the fourth branchial clefts. They seem to occur infrequently in man (Müller). Besides these normal structures not rarely rests of thymus tissue are found in the thyroid gland, or about it.

Ciliated Vesicles.—Vesicles lined with ciliated epithelium are occasionally found, not only in the thyroid, but in the parathyroid, or thymic lobule (see Fig. 4713), or in the thymus; they may give rise to cysts. Their content is a clear fluid, quite different from the colloid. They are probably derived from the original pharyngeal or branchial diverticulum, and persist as does the thyroglossal duct.

Chemistry.

Until 1896 the thyroid was studied frequently to learn something of its chemistry, because as a gland with internal secretion it seemed possible that this unknown secretion might be found. It was learned that it was rich in the various extractives, indicating metabolic activity, and that it contained a nucleo-proteid and a globulin of some interest. Fraenkel thought he had isolated an active principle in a crystalline, alkaloid-like body, apparently belonging to the guanidin series. Baumann in 1896 succeeded in isolating the real active principle in the iodine compound, *thyroiodin* or *iodothyrein*. This, according to Baumann, is a brownish, amorphous compound, remarkable for its resistance to chemical and physical agencies; it can be boiled for days with ten per cent. sulphuric acid or undergo prolonged digestion with gastric juice without alteration. This explains its successful use per os therapeutically. It is almost insoluble in water; in alcohol it dissolves with difficulty. It manifests no proteid reactions, and in the purest specimen that Baumann was able to obtain, he found 9.3 per cent. of iodine, which is probably below the true proportion. Working with Baumann, Roos subjected it to physiologic and therapeutic tests that showed it to be the active principle of the gland. There seem to be no essential differences in the substance as obtained from either human glands or from the lower animals. However, the variations in the amount of iodine found in the glands of individuals in health is great, but it may be stated that in goitrous districts the amount of iodine is much less than in the places where goitre is rare. This is shown by the accompanying table.

The manner in which the iodine is combined in the thyroiodin is still unknown, although according to the work of Oswald it is preponderatingly, if not entirely, united to aromatic groups. However, it is known that the iodine is combined in a non-proteid body, the thyroiodin, which in turn is combined with a proteid, forming the

Place.	Dry weight of glands.	Iodine per gram in milligrams.	Total milligrams iodine.	Frequency of goitre.
Freiburg	8.20	0.33	2.50	Endemic.
Hamburg	4.60	.83	3.83	Not endemic.
Berlin	7.40	.90	6.60	Not endemic.
Chicago	5.37	2.10	10.79	Not common.
Boston and New York	4.47	2.64	11.80	Not common.
Baltimore	5.41	2.36	12.76	Not common.
Montreal	4.49	2.40	10.77	Not common.

thyroglobulin. This thyroglobulin contains 1.6 per cent. of iodine, and is found entirely in the colloid of the gland, but it is not the sole ingredient of the colloid, which contains a neucleoproteid also. Oswald believes that the iodine is united with the globulin either just as it is excreted from the cells or after it is in the acini; a thyroglobulin devoid of iodine may be found under some conditions. The thyroid of new-born infants, as well as of calves and other young animals, is either devoid of demonstrable quantities of iodine or contains but traces, and in them a colloid containing globulin free from iodine is found. Many experiments have shown that the functional activity of the thyroid, whatever it may be, is due entirely to this iodine compound, acting not as iodine or as an iodide, but specifically as thyroiodin. Whatever effects can be obtained by administration of the entire thyroid can be as well obtained with the pure thyroiodin. There is no evidence of any function on the part of the nucleoproteid. The thyroid, then, differs from ordinary glands simply in having the lymph vessels for its excretory ducts. What becomes of the thyroiodin after it is eliminated from the gland is unknown, but it is thought that the iodine is returned to the gland after it has performed its functions, to be rebuilt into thyroiodin. Iodine cannot be found in the other organs in appreciable quantities, although infinitesimal quantities are said by some observers to be quite widespread. If large quantities are administered to animals iodides appear in the urine (Blum), but according to Oswald physiological doses do not lead to its appearance in quantities that can be detected. Nor is it known in what manner it is taken up by the gland, whether from unknown tissue iodides, or organic iodine compounds, or from minute traces that exist as iodides in the water and air. It is known that when iodides are administered therapeutically the colloid becomes richer than normal in iodine, but it is questionable if the iodides are converted into thyroiodin before exerting their effects. Administration of bromides does not influence the iodine content of the thyroid, and there is no storage of bromide in the gland. Administration of pilocarpine does not increase the thyroiodin.

The colloid seems to vary greatly in its composition, but as a rule the more colloid there is in a gland the less the proportion of iodine, so that the total iodine content is kept nearly constant under normal conditions. This is far from true in the goitres, for some are nearly devoid of iodine, while others contain much greater quantities than normal. In goitres, while in a way the amount of iodine increases with the amount of colloid, yet this is only partly true, for the greater the amount of colloid the less its proportional amount of iodine. Oswald has found that in colloid goitres this is due to the accumulation of a globulin in the colloid that differs from thyroglobulin in not possessing any iodine. In the parenchymatous form of goitre, in which microscopically the enlargement is due to the development of enormous amounts of epithelium with very little colloid, the amount of colloid in each part of gland tissue is much lower than normal, although the total amount will usually approximate that found in the normal gland. The scanty presence of iodine is not due to an inability of the gland to combine it, for in the goitrous thyroids of people who had received iodides before death the amount of iodine has been found to be large. In exophthalmic goitre the proportional amount of iodine has generally been found to be small, although here, too, the gland has been found by Oswald to be capable of utilizing iodine administered therapeutically. The colloid from goitres, so far as it contains iodine, possesses the same physiological properties as the thyroglobulin from normal glands, but in less quantity. If free from iodine it is entirely inactive (Oswald).

According to Gautier the thyroid contains about 0.75 mgm. of arsenic in each 100 gm. of substance, and is the richest in arsenic of any of the tissues of the body. He considers that it is bound to the nucleoproteid of the colloid, perhaps substituting for phosphorus, and that it is of physiological importance, especially in relation to sexual phenomena. The amount of arsenic is too small to cause confusion in medico-legal matters.

Physiology.

Most of our knowledge of the action of the thyroid gland is based upon the changes observed in man and animals when they are under one of two conditions, which are:

1. When the animal is receiving less than the usual amount of secretion from the thyroid, as in extirpation experiments.
2. When the amount of secretion in the body is above normal, as when thyroid extract is being administered.

These observations include not only the results obtained by experiments, but also those obtained from clinical observations, since here the symptoms are due sometimes to hypo-activity, *e.g.*, myxœdema and cretinism; or to hyperactivity, as sometimes in therapeutic use of thyroid, or after operations, and possibly in exophthalmic goitre.

In the first case when the subject is receiving less than the full influence of the thyroid gland, we observe symptoms that may be divided into nutritional and nervous.

(*a*) The nutritional changes seem to be of such a nature that the metabolic changes throughout the body do not proceed to their full extent, or are reduced in rate, and the power of cellular reproduction is altered. As a result of the first the connective tissues stop in their metabolic processes just short of completion, leaving them, as Semon suggested, in an embryonic condition, that is, in the form of myxomatous tissue, which is their embryonic representative. From this results the condition of the skin seen in myxœdema. This change seems not to be confined to the subcutaneous tissues, but is a general change, for Halliburton has shown that in the blood of monkeys rendered myxomatous as a result of thyroidectomy, there is demonstrable a considerable quantity of mucin. Because of the failure of complete cell reproduction, or an alteration in the process, we observe a change in young animals, quite analogous to cretinism in children. Besides this, there is a decrease in the gas exchange of the blood, for in thyroidectomized animals the amount of carbon dioxide is increased and the oxygen diminished until the arterial blood may be below the normal venous standard. The urine indicates that all metabolic changes are lessened. Oligocythæmia is usually marked.

(*b*) The nervous system is apparently greatly affected, the most marked symptoms from this source being those due to the excitation of the muscular fibres, viz., twitching, tremors, and spasms. These seem to proceed from the lower centres, for Horsley has observed them in monkeys subjected to ablation of the motor cortex, and Munk found that they were not affected by division of the cord, while Schiff showed that they were not of peripheral origin by finding that section of the motor nerves stopped them. Degenerative changes have been found in the anterior horn ganglion cells of thyroidectomized dogs. Later, these symptoms are followed, if the animal survives, by a lessening of the power of voluntary action, as well as by loss of sensation. The thermotaxic apparatus is also affected, so that the body temperature falls three or four degrees below normal. Lorrain Smith has observed that the reaction of thyroidectomized animals to

changes of temperature is abnormally rapid, so that if such an animal is exposed to cold the production of carbonic acid is increased immediately, instead of being delayed for some time as in normal animals. Moreover many of the symptoms of athyreosis are alleviated by artificial heat.

The clinical picture resulting from the above-described changes is referred to as *cachexia strumipriva*, or *thyroid cachexia*.

When the thyroid preparations are administered to animals experimentally, or to man therapeutically, opposite effects are produced.

(*a*) *Nutritional.*—Metabolism throughout the body undergoes an increase, shown best by the urine. This is considerably increased in quantity; it contains a greater amount of urea as well as chlorides and phosphates. At the same time the weight of the patient decreases, particularly if it is above normal on account of fat deposition. This decrease in weight is constant and considerable, and, according to Wendelstadt, but one-sixth can be attributed to destruction of proteid, as indicated by the urinary nitrogen, the rest being due to loss of water and of fat through increased oxidation. In young individuals of stunted growth the height is often increased.

(*b*) *Nervous.*—Of these, palpitation of the heart is often one of the most prominent. With it come headache, nausea, and vomiting, if the dose is very excessive, and the heart may weaken to a dangerous degree. The patient is excitable, irritable, and often sleepless. Diarrhœa often sets in, and in some patients taking thyroid extract continuously in myxœdema and cretinism the condition of the bowels is found a good guide to the amount of the extract to be administered. Sometimes glycosuria is produced, which in a few instances is said to have developed into a true diabetes mellitus. Schaefer has also shown that if thyroid extract is injected into the veins of healthy dogs there follows an immediate fall of blood pressure due to general vascular dilatation.

It is to be noted that the symptoms that are attributed to the thyroid may be due in part to the parathyroids, which according to some experiments seem to be really more essential to the individual than the thyroid itself. There is a tendency to attribute much of the nervous manifestation to the parathyroids, while the metabolic processes are credited to the thyroid. According to Hutchinson, removal of the thyroid alone probably causes myxœdema, while removal of the four parathyroids causes the acute tetanic symptoms. (See article on *Parathyroid.*)

From the facts noted above have been developed two theories to explain the action of the thyroid. One assumes that the thyroiodin that has been excreted by the gland neutralizes a toxic material, either while passing through the thyroid in the blood, or, more probably, while circulating in the blood stream of the body as a whole. This hypothetical toxic substance may come either from alimentary absorption, or from metabolism, as an abnormal or normal intermediary or end-product. The other theory advocates the idea that thyroiodin is essential in normal metabolism. It suggests that thyroiodin may be essential for certain of the normal cell processes, much as calcium salts are involved in the coagulation of the blood. Either of these theories may be applied to most of the known facts, but neither is entirely satisfactory. One of the strongest evidences in support of the antitoxic nature of thyroiodin is furnished by Blum, who found that ninety-six per cent. of his thyroidectomized dogs died when fed upon meat, while but sixty per cent. died when they were fed upon milk. Dogs that were getting along well on a milk diet developed symptoms of athyreosis when fed upon meat. Hence it is considered by him that symptoms that follow thyroid extirpation are produced by substances formed by the meat in the gastro-intestinal tract, which are produced in less quantity by milk, and which the thyroid normally neutralizes. It is, however, probable that milk contains thyroiodin, for young calves are said by Oswald to have no iodine in their thyroids, and he believes that the deficiency is supplied by the mother's milk, for, as is well known, the maternal thyroid is hypertrophied during gestation and lactation. He is inclined to think that if there is a toxin it is one of the normal intermediary products of metabolism which does not undergo its usual transformations because of the general decrease in metabolic activity.

That there is a close relation between the thyroid and the reproductive functions, particularly in the female, is beyond question. This is shown by its enlargement during menstruation and pregnancy, its early atrophy after the menopause, its greater size in the female, its tendency to develop goitre during pregnancy, and the loss of sexual appetite in many of the thyroid diseases. It is stated that from eighty to ninety per cent. of all cases of goitre and eighty-six per cent. of the cases of myxœdema are in women, and Graves' disease occurs chiefly in females. Halsted observed that bitches that had lost part of their thyroids, but not enough to give rise to symptoms, when impregnated showed evidences of athyreosis as the time of parturition approached, which disappeared soon after the litter was born. Further, in all of the pups of these litters the thyroid glands were many times the normal size of the glands of pups of the same weight. Just what part the thyroid plays in pregnancy is unknown.

It may be that it hypertrophies to supply the needs of the fœtus, which, as we have noted, does not form thyroiodin in its thyroid, and whose needs must be great if thyroiodin is necessary for cell growth. As to the hypertrophy of menstruation, Gautier claims to have demonstrated both iodine and arsenic in menstrual blood as well as in the thyroid, and he believes that the latter supplies the former. It has been thought by some that the thyroid may play a rôle in the production of puerperal eclampsia. One writer states that hypertrophy of the thyroid is absent in eclampsia, and ascribes this disease to thyroid inefficiency. In this connection the experiments of Blum are of interest. He found that in the dog thyroidectomy was followed by albuminuria almost constantly, sometimes with hæmaturia, and accompanied by marked renal lesions if the animal survived long enough to develop them. Alterations in the central nervous system, affecting chiefly the Nissl bodies, have been described by Blum and other observers.

Lange sums up the relation of the thyroid to pregnancy as follows: A physiological hyperplasia like that observed in the thyroid in pregnancy has never been found in the kidney at this period. Pregnant animals need a larger thyroid than those not pregnant. When a piece of thyroid just sufficient to continue life in a non-pregnant animal, is allowed to remain in a pregnant animal, an insidious kidney disease develops, one that may result in convulsions and coma, which are not relieved by thyroiodin, and which are distinct from the convulsions of tetany.

The marked atrophy of the thyroid in old age has been regarded as indicating some possible influence on senility. More probably it is related to the decline of sexual life. It is interesting to note that the thyroid arteries are prone to show very early sclerosis, often before other vessels are at all affected. The decrease in red corpuscles after thyroidectomy is probably the result of the decreased activity of the blood-making organs, or it is dependent upon an increased destruction by toxic substances. The decrease is not, as was once thought, an indication of hæmatopoietic properties of the thyroid. Another old theory, probably baseless, was that the thyroid was a reservoir into which the carotid blood might be shunted to produce cerebral anæmia and thus favor sleep.

Pathology.

Malformations.—Because of its manner of development the form of the thyroid is very inconstant, and this matter has been in part discussed under the subject of anatomy. The commonest alterations from the usual

form are absence of the pyramids, or of the isthmus; the latter may also be of peculiar shapes, and it has been known to pass between the trachea and the œsophagus. Hypoplasia, and even total absence, may be observed in cretinism, and it is usually absent in acephalics. Hektoen has recently reported a case of dwarfism, related to the type of achondroplasia fœtalis, in which the very small gland was nearly devoid of epithelial elements, and contained no demonstrable iodine. Unilateral glands are uncommon. Many abnormalities of form are produced by the formation of colloid cysts, and by the cicatricial contraction of healed cysts.

The *thyrolingual* duct may fail to become obliterated, remaining as a canal which extends for a longer or shorter distance from the foramen cœcum; occasionally residual portions of this duct become dilated into cysts of varying size. These cysts may open and form a median cervical fistula, usually opening below the cricoid cartilage, and lined either with stratified or with columnar epithelium. Lingual dermoids and tumors at the base of the tongue have been traced to this origin.

Accessory thyroids are of a structure identical with that of the thyroid, although they sometimes reproduce rather the fœtal than the adult type. They are far from constant in occurrence, or location, or numbers. In general they are located in an isosceles triangle which has its base at the lower jaw and its apex at the aortic arch. The most frequent location is in the vicinity of the hyoid bone, and they have been found within the bone itself. Many of them are attributable to remnants of the diverticulum that ordinarily forms the pyramids, often replacing this structure. Of particular practical importance are those found within the larynx or trachea, for these may give rise to marked symptoms. Thiesen found in the literature 10 positive and 2 doubtful cases of this sort, 8 of which occurred in Germany. Of 91 benign intratracheal growths which Bruns in 1898 collected from the literature, 7 were of thyroid origin. The structure is usually the same as that of normal thyroid, and, like it, contains colloid. Accessory thyroid may be the result of inclusion of an accessory thyroid lobule in the larynx or trachea in intra-uterine life, or the membrane between the rings of the trachea may be penetrated by adherent thyroid tissue during later life. Usually the growth is located on the posterior or on the lateral wall, being attached by a pedicle to the thyroid. Seven of the 10 cases were in women, and were detected usually between the fifteenth and thirty-third years. In Thiesen's case dyspnœa was increased by pregnancy. In only 2 cases did goitre coexist. One case of thyroid tumor at the base of the tongue is of particular interest, in that its removal was followed by symptoms of myxœdema, which were relieved by thyroid therapy (Shurley). Here it would seem probable that atrophy of the gland proper had resulted in a compensatory hypertrophy of the remnants of the thyrolingual duct.

Circulatory disturbances of the thyroid are prominent because of its great vascularity, but they cause relatively little trouble unless the gland is already enlarged, when the added size may be of importance.

Passive congestion may occur in heart disease and from pressure on the cervical veins, but it is rarely evident, has no apparent effect on the function of the organ, and it seems not to cause structural changes of moment.

Active hyperæmia is frequent, usually physiological, and it is held responsible for the visible enlargement of the gland in menstruation, pregnancy, sexual excitement, and at puberty. However, it is not always easy to determine how much of the enlargement is due to the vascular dilatation, and how much to hypertrophy of the gland elements or to increased production of colloid, since all these may go together. At times it may be so great that a distinct bruit can be heard over the gland; this is particularly the case in Graves' disease. In various forms of goitre (*q.v.*) hyperæmia is present; in fact, a vascular form has often been mentioned in the literature, although it is very doubtful that there is such a thing as a real goitre produced solely by vascular enlargement. Probably the active hyperæmia of sexual origin is the same as that of other glands during physiological activity. Sudden hyperæmia may cause severe, even fatal attacks of dyspnœa when the glands are goitrous. So in pregnancy dyspnœa is always increased if it existed previously, or it may appear first at this time.

Infarction does not seem to occur, the circulation being too free. If emboli lodge there they seldom seem to cause effects, for even in pyæmia, miliary tuberculosis, and vascular dissemination of malignant growths the thyroid escapes more often from secondary lesions than do other organs, particularly if the great amount of blood that it receives is considered.

Hemorrhage is a prominent feature of the goitres, but it also seems to occur even in the normal gland. The red cells are preserved for a long time in the colloid, but eventually give rise to accumulations of pigment and cholesterin crystals, which latter may be very abundant. Any trauma of the thyroid is likely to give rise to hemorrhage, either into the vesicles or into the periglandular tissues. Large intraglandular hemorrhages may soften and lead to cyst formation, or become infected.

Progressive Changes.—Thyroid tissue has great vitality, and there is no other gland that can be transplanted so successfully. As the secretion is removed by the circulation any transplanted portion can functionate, and the treatment of myxœdema was first successfully accomplished by grafting. An important fact, in view of the study of cytotoxins, is the following: transplantations can be made from one species into another with perfect results. For example, sheep thyroid has been implanted into man and has cured myxœdema, showing that the secretion is practically the same in the different species. At first, the graft undergoes considerable necrosis and is partly absorbed, but some cells remain alive, and from these develop thyroid tissue in proportion to the needs of the body, for thyroid tissue has almost unequalled capacity to undergo compensatory hypertrophy. Grafts removed after four and one-half years have been found of the same structure as normal or hyperactive thyroid.

During hyperactivity, whether compensatory or not, the gland shows a decrease in the amount of colloid in the vesicles, as if it were being absorbed as fast as formed. The epithelial cells increase in size, either because of lack of pressure from colloid or because of formative or secretory stimuli, and the walls are thrown into folds so that the secreting surface is increased. Such changes as this were observed by Halsted in remnants of glands left after partial thyroidectomy, and they are seen in many cases of exophthalmic goitre, supporting the theory of the origin of this disease in thyroid hyperfunction. But a small remnant of the gland needs to be left in most cases to enable the demands of the body to be met, and not only normal gland tissue, but accessory thyroids and even tumor metastases, may functionate adequately.

Hypertrophy of a simple nature seems to be the process which causes many goitrous enlargements, and it is undoubtedly physiological in many instances, in response to some unknown demand of the body for increased activity. It is probably in such cases that operation is particularly likely to be disastrous. In acromegaly, associated with disease of the hypophysis, the thyroid is often enlarged, as it also is in many cases of giantism. The hypertrophy of pregnancy is undoubtedly physiologic.

Retrogressive Changes.—*Atrophy* occurs prominently in old age, and is accompanied by a relative increase of the connective tissue, and a decrease in the amount of both colloid and epithelial elements. This is without evident effect on the individual, and seems to be secondary to decreased needs of the organism. It has been suggested that it may have a relation of primary importance to senility. In this connection it is to be noted that sclerosis of the thyroid arteries seems to occur particularly early in life. In youth atrophy sometimes gives rise to cretinism, while in adults it may lead to myxœdema. However, one may find very small thyroids