MORPHOLOGICAL STUDIES IN EXPERIMENTAL CRETINISM.*

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In making a study of the physiology of experimental cretinism, suggested to me by Professor A. J. Carlson, of the University of Chicago, a large amount of material became available for morphological observations, and it is with this phase of the subject that the present paper is concerned.

Several members of litters of very young rabbits, from two to three weeks old, weighing from 150 to 250 gm. each, were thyroidectomized, while at least two members of each litter were kept for controls. All were weighed at regular intervals for the charting of growth curves. The operative technique of Hofmeister was followed, in the main. A median incision of about 1.5 cm. in length was made to center over the prominence of the larynx. With fine pointed forceps the inferior pole of the thyroid was freed from the laryngeal nerve, then carefully separated upward. The single thyroid artery is either ligated before division, or crushed with the forceps till coagulation within allows a division without ligation. This last procedure was very satisfactory in cases of young rabbits with relatively small arteries. The deeper superior pole was followed laterally and superiorly till its sheath was exposed, and was then separated from the connective tissue. After freeing the median superior attachment from the thyroid cartilage, this lobe together with the connecting isthmus was reflected over the remaining lobe, which was separated in a similar manner. Thus the whole thyroid apparatus was removed. At the superior poles of the glands, considerable difficulty was encountered on account of the intimate relation of the thyroid capsule to the thyroid cartilage. As is well known, the external pair of parathyroid glands are lateral, or sometimes inferior to and separate from the thyroid lobes. These, while usually seen during the operation, were rarely touched or disturbed in any manner. The whole operation, done aseptically, and under light ether anesthesia, rarely required more than one half hour. The operative procedure at the age of the animals used was well borne, and in no way influenced subsequent growth. This is shown

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1 This work was undertaken primarily to establish a biological test for the active principle of the thyroid glands. The preliminary work was largely done in the Hull Physiological Laboratory of the University of Chicago.
by the growth curves of the rabbits which at exploratory examination, or at autopsy, revealed various sized nodules of thyroid tissue at the superior line of attachment of the thyroid capsule to the cartilage. These animals grew as rapidly and normally as the controls, and demonstrated, in addition to the innocuousness of the operation, the fact that surprisingly small nodules of hyperplastic glands, under these conditions, fully supplied the physiological need.

The completeness of the thyroid removal could never be absolutely determined at the time of the operation. Yet, after a few weeks, certain diagnosis of the animal’s thyroid apparatus can be made from the growth curve and general appearances. While the term cretinism has been applied to the condition found in congenital absence of functioning thyroid, and while some may criticize the application of the term to a postnatal operative thyroprival cachexia, the rabbits are essentially cretins, showing great depression of rate of growth, are of pot belly type, with scaly skin, coarse thin hair, and are quite slow and awkward. They fully satisfy the description of cretin rabbits as given by Moussu, Gley, Hofmeister, and Haushalter and Jeandelize. Leonhardt apparently failed in all, while Blumreich and Jacoby failed in several cases, to effect a complete thyroid removal. This is apparent from a study of the increase in weights of their animals after thyroidectomy. Hofmeister obtained several cretins. He does not state how many failures he had, but he does state that not all of his thyroidectomized rabbits developed into cretins. Moussu, and Haushalter and Jeandelize described two or three cases each, and from reading their reports one is led to believe that no difficulty is to be encountered. Bensen operated only on young adult rabbits, and while his series is not strictly comparable to that reported in this paper, he nevertheless obtained definite morphological changes in certain organs.

The following protocols are taken from a series of about twenty-five autopsies, and comprise only those of completely thyroidectomized animals. The histological findings, which are constant and characteristic, will be given in detail in a single case, and in abbreviated form in the remaining eleven cases. None of the animals was killed for the purpose of morphological study. A large number were autopsied immediately after spontaneous death, following a rapid fall in temperature, and apparently due to the cachectic condition of the animals. Two or three were accidentally suddenly
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killed by intravenous injections of normal defibrinated rabbit blood, which was first filtered through sterile gauze to remove clots. The histological picture of these animals differed in no essential respect from those dying spontaneously. For histological controls unthryoidectomized rabbits of corresponding ages were used. The tissues were all fixed in formalin, hardened in alcohol, and stained with hematoxylin and eosin.

PROTOCOLS.

Rabbit 54.—Albino, female; weight, 200 gm. December 9, 1911. Thyroidectomized. Weight of control 54 A, 193 gm. January 4, 1912. Weight, 558 gm. Weight of control, 814 gm. The hair of the cretin is ruffled and falling out badly; skin, scaly and dry. The abdomen is distended, and of the pot belly type. The animal appears to have a good appetite, yet moved about but little. April 6, 1912. Weight, 879 gm. Weight of control, 2011 gm. Nothing unusual was observed. April 7, 1912. Reported dying by attendant. Autopsy was made while the body was still warm, within one half hour after death.

Autopsy.—The skin is dry and scaly, and the subcutaneous tissues are moist and glistening. The abdomen is distended, but there is no gas in the intestines. 2 c.c. of clear peritoneal fluid was obtained which coagulated within fifteen to twenty minutes to a cloudy, firm clot. No signs of infection or peritonitis. The lungs are congested, the liver is pale in color, and on section the kidneys seem to be congested. The thymus is of good size. The ovaries are large. The parathyroids are pale. There are no macroscopic signs of thyroids. The cerebral meninges are congested and the hypophysis cerebri enlarged. The bone marrow is firm.

MICROSCOPIC EXAMINATION.

Heart.—The myocardium presents a remarkable picture of degeneration of the individual muscle fibers. The fibers, in cross section, appear throughout to consist of a single layer of peripheral sarcostyles surrounding a central clear area which may or may not contain a nucleus. The muscle cells have not only lost all but the peripheral layer of sarcostyles, but in addition are swollen to two or three times the size of the normal heart muscle fibers. In areas this swelling is not marked, yet the central sarcostyles have disappeared, being replaced by clear non-staining areas. There is no indication of fatty degeneration. In longitudinal section of the fibers, the fibrillae are very prominent; the longitudinal striation of the fibers being especially marked; the longitudinal striation of the fibers being especially marked; the longitudinal striation of the fibers being especially marked; the longitudinal striation of the fibers being especially marked; the longitudinal striation of the fibers being especially marked; the longitudinal striation of the fibers being especially marked. These areas of the section also reveal the sheen character of the fibers. The cytoplasm takes a good stain with eosin, and the nuclei are also well stained and normal in appearance. There is edema of the interfibrillar tissue.

Lungs.—The pleura is normal. The arterioles and capillaries are congested, while the larger arteries are empty. The veins are greatly distended. The bronchioles are practically all collapsed, the columnar epithelium of which is uneven, ragged, granular, vacuolated, and partly desquamated. The alveoli in many areas particularly about the bronchioles are atelectatic, while those about the periphery are emphysematous.
Liver.—The intimal walls of some of the central veins are thickened, with dilated lumina. Connective tissue about the bile ducts is loose and wide. The liver cells are, for the most part, two to four times as large as the normal liver cell. In scattered small areas are found cells of about normal size and appearance. The larger cells are paler in color, somewhat transparent, with relatively few, very large coarse granules in the non-staining matrix of the cells. Some appear to be confluent, with no separatory walls. Nuclei occur largely in pairs, are large, and sharply stained. The largest and palest cells have pale nuclei, or none at all. No fatty degeneration is shown. The cells of the section, as a whole, have a washed out appearance.

Spleen.—A condition of hyperplasia of pulp tissue and hypoplasia of Malpighian corpuscles is found. There are a great many large and small phagocytes in the pulp sinuses, the larger of which are filled with cell fragments and hemosiderin granules. The spleen is also congested.

Pancreas.—The secretory parenchyma appears normal and sharply staining. The islands of Langerhans are very distinctly marked off from the rest of the tissue, and are made up of an increased number of enlarged, well staining cells. The nuclei vary from large vesicular to small and dense types.

Kidney.—The capsule is normal. The larger blood vessels are surrounded by loose areolar tissue of decidedly edematous appearance, which immediately about the vessels takes a pale blue stain. The glomerular tufts are congested; the glomerular epithelium is well stained, yet vacuolated in some areas and granular in others. The nuclei are sharply stained. The cortex shows scarred areas in which the parenchyma is replaced by connective tissue. Nuclei of the cells of the tubules, are, for the most part, well stained, yet in some small areas are very pale, or absent entirely. Cytoplasm is decidedly granular and ragged. In the cells of certain of the convoluted tubules are dense and deeply eosin-stained droplets of colloid degeneration. Some vacuolation is also found in the cortex. The collecting tubules are lined by excessively swollen cells which exhibit a nucleus and a sharp cell border, and are without demonstrable cytoplasm.

The transitional epithelium of the pelvis of the kidney and of the urinary bladder presents the same picture of swollen, clear, vacuolated cells.

Skin.—The horny layer is scaly, rough, and varies greatly in thickness. The corium is wide and loose, i.e., edematous, without signs of mucoid appearance. The edematous corium grades rapidly into the dense subcutaneous tissue beneath. The blood supply is poor.

Esophagus.—The muscle shows some atrophy of fibers. Owing to edema, the areolar tissue between the muscle and epithelium is at least twice the normal width. Some fat cells are found in the areolar tissue. The epithelium appears normal. Several lymphoid nodules are found.

Large Intestine.—The individual cells of the outer muscular coat are separated from one another by spaces bridged across by cytoplasmic processes resembling protoplasmic bridges. Under oil immersion this appearance is found to be due to a continuous row of vacuoles encircling the periphery of the fiber. The muscle cells themselves are degenerated to a varying degree. Some, cut in cross section, are very pale and finely granular; others are dense and appear normal. The pale cells are usually very large, i.e., swollen to two or three times the normal size.
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The mucosa contains great numbers of goblet cells which, in the base of crypts, form a continuous layer.

Trachea.—The muscle is the same as in the esophagus. The areolar tissue between the cartilage and epithelium is abnormally wide and edematous. The blood and lymph vessels are much distended. The epithelium appears normal.

Ovary.—Cross section of the ovary measures 5 by 7 mm. Nine follicular spaces can be seen by the unaided eye. These are from 1 to 2 mm. in diameter. Germinal cortical epithelium is cuboidal or low columnar, the cytoplasm of which is for the most part vacuolated by serous imbibition. The nuclei lie towards the distal ends of these cells. Many of the cells composing the cords are vacuolated, others have clear undefined areas similar to those of the cortical epithelium. Primitive follicles are fairly numerous, but the nuclei of the ova are undergoing karyolysis. The large follicles make up a large part of the sections. There is relatively little stroma. Numerous germ hills are found in the large follicles, yet no normal ova are found in the entire section. In several of the medium sized follicles, the ovum is replaced by a disorganized cell mass in which are found bands of hyaline material apparently representing degenerated zona pelliculide. In one instance, a complete ring of this material is seen to surround a mass of degenerating follicular cells in an early necrotic stage. The large follicles are filled, for the most part, by a thin, hyaline-like material. One small follicle is found filled with closely packed, small, round cells, which resemble lymphocytes.

Oviduct.—The stroma and muscle appear normal. The epithelial cells are coarsely granular and some indicate mucoid degeneration from the typical reaction with hematoxylin.

Mesenteric Lymph Glands.—Sections present the general picture of lymphoid hyperplasia. Numerous, isolated, fat cells are found in several of the lobes.

Adrenal Glands.—Cells of both the cortex and medulla are rather more vacuolated than normally. The ratio of the width of the medulla to the width of the cortex is greater than normally, apparently depending upon an absolute increase in the medullary area. Müller-formol fixation shows a large amount of chromaffin tissue. Cords of cortical cells interweave with cords of medullary cells at the boundary zone.

Bone Marrow.—The tissue is of the fatty type, with normal fat cells. Leucogenetic centers (Bunting) predominate over erythropoietic centers. In the former the center is characterized by a few large myelocytes surrounded by polymorphonuclear leucocytes which show fragmentation and degeneration. Megakaryocytes show generally karyolysis and cytolysis.

Parathyroid Glands.—The cytoplasm of most of the epithelial cells is poorly stained, i.e., chromophobic. At the same time definite vacuoles of nuclear size are plentiful. The cells are enlarged and swollen. There is no congestion, and no sign of either acinus formation or colloid.

Hypophysis Cerebri.—This organ shows three areas corresponding to the pars anterior, the pars intermedia, and the pars posterior. The pars anterior is rounded and constitutes by far the major part of the gland. The cells are grouped into clumps and cords. The majority of these cords take a light pink stain, while a small percentage are eosinophilic. The pale staining cells show in some cases definite vacuolation, in others irregular clear areas, with ragged boundaries. The pars intermedia is not sharply separated from the pars anterior,
The cells are of a type similar to the eosinophilic cells of the pars anterior. Neither vacuolation nor appearance of neutrophilic or chromophobic character occurs in the cytoplasm. All cells in this zone are strikingly alike and constant. No colloid masses are found. The pars nervosa is infiltrated on its intermediary border by single cells or small groups of cells from the pars intermedia. The area of infiltration is somewhat pyramidal, with its base to the pars intermedia. On the border line between this infiltrated area and the nervosa proper is found a single duct, not unlike a single zymogenous pancreatic acinus in appearance. It consists of eight cells of low columnar or pyramidal type, with densely staining nuclei at the base of cells. The cytoplasm is finely granular and stains a deep pink with eosin. The pars nervosa, aside from a single doubtful instance, shows no sign of colloid. The exception is a small, nucleus-free, hyaline mass.

In order to avoid repetition, protocols of the rest of the series will be given in condensed form, except in cases of deviation from the types already described.

Rabbit 54 B.—Male. January 2, 1912. Thyroidectomized. Weight, 264 gm. Weight of control 59 A, 237 gm. April 22, 1912. Weight, 870 gm. Weight of control, 1,910 gm. This animal was unintentionally killed by an intravenous injection of 5 c.c. of defibrinated normal rabbit blood. Autopsy performed immediately. The litter of which this rabbit was a member had been raised in a hutch newly floored with heavy sheet zinc which became more or less polished by the rabbits. The thyroidectomized rabbits, 54 B, 55, and 57, developed muscular exhaustion in the adductors of the fore legs, so that they were unable to support themselves, but lay on their chests, turtle fashion, with legs extended laterally. The normal rabbits of the same litter and in the same hutch were not affected.

The skin is scaly and dry, and the hair is rough. The subcutaneous tissues are very pearly in appearance. The abdomen is distended. 8 c.c. of clear peritoneal fluid were collected. This coagulated to a firm, turbid clot. 1.75 c.c. of pericardial fluid were collected, which did not coagulate on standing. The heart is small, with a white dotted border at the base of the ventricles, also many small clear blisters are seen here. The auricles are still irritable and beating when dropped into formalin. The lungs appear normal. The thymus is small. The liver is spotted with brown flecks. The spleen is normal. The kidney pelvis is filled with a clear viscous material; the cortex is slightly congested. The adrenals and testes appear normal. The parathyroids are small. The bone marrow is dark and firm. Hypophysis measures 5.5 by 4 by 4 mm. Hypophysis of the control rabbit, which weighs 2120 gm., measures 4.5 by 3.5 by 3 mm.

MICROSCOPIC EXAMINATION.

Heart.—Extreme sarcostyle degeneration, with edematous fibers.

Lungs.—Congestion, atelectasis, bronchial collapse, emphysema in areas, hemorrhage.

Liver.—Swollen, binuclear cells; slight karyolysis. No fat.
Spleen.—The pulp is hyperplastic, and there is an excess of pigmented phagocytes. Hypoplasia of the Malpighian corpuscles.

Pancreas.—The islands of Langerhans are hyperplastic and hypertrophic.

Kidney.—Granular degeneration of the cortical epithelium; granular degeneration and hydropic imbition in the cells of the collecting tubules, pelvis, and urinary bladder.

Skin.—Edema of the corium. No mucoid stain.

Esophagus and Trachea.—The submucosa is edematous. The muscle shows two types of degeneration: (1) hyaline and (2) vacuolation.

Intestine.—Edema of the submucosa. Muscular degeneration. Vacuolation and swelling of the ganglion and sustentacular cells of Auerbach's plexus.

Mesenteric Lymph Glands.—Hyperplasia; fatty infiltration.

Adrenals.—Medullary hypertrophy; fatty cortex; congestion.

Testes.—Karyolysis of the germinal cells. No mature spermatozoa are found. The tubules are wide, but have a scanty cellular content. The interstitial cells of Leydig are large and plentiful.

Parathyroids.—The cells are vacuolated and somewhat swollen. No acini; no colloid formation.

Thymus.—Regressive type. Hassal's corpuscles are larger and more prominent than normally.

Hypophysis Cerébri.—The anterior lobe is congested. Fatty and serous vacuolation of cells. Some karyolysis. Relatively few eosinophiles. The cells of the pars intermedia are somewhat vacuolated. Neither colloid nor acinus formation is seen in any part of the whole organ.

Bone Marrow.—Fatty, inactive type; leucogenetic centers predominate over erythropoietic centers. The megakaryocytes are few and degenerating.

Striated Muscle (Pectoral).—Longitudinal striation is much more prominent than transverse striation; there are many areas of areolar tissue with only scattered single fibers, indicating absorption of muscle tissue. Some fibers show vacuolation, others are hyaline in character.

Cervical Adipose Tissue.—Shows serous atrophy.


Autopsy.—The hair and skin are typical. The subcutaneous tissues are pearly. 9 c.c. of clear, reddish, peritoneal fluid. Excessive pericardial fluid. The adrenals are larger than normally, 12 by 7 by 3 mm. There is no macroscopic thyroid. The hypophysis measures 6 by 4 by 3 mm.

Microscopic Examination.

Heart.—Extreme central sarcoptyle degeneration.

Liver.—The cells are swollen. There is fat in the mid and central zones. Considerable hemosiderin.

Lung.—Atelectasis; bronchial collapse; slight emphysema; vascular dilatation.


Pancreas.—The islands of Langerhans are enlarged.

Skin.—The scaly layer is deeply stained with eosin. The corium is edematous and gives a mucoid stain with hematoxylin. Beneath this zone the blue color fades and passes gradually into the usual pink cytoplasmic stain of connective tissue.

Trachea and Esophagus.—There is marked edema in the submucosa which takes a distinct bluish stain about the esophagus. The muscle is vacuolated with edematous connective tissue separating the individual fibers.

Ovary.—Cystic degeneration of the follicles; karyolysis of the ova; germinal epithelium; hydropic.

Mesenteric Lymph Gland.—Slight lymphadenitis. The phagocytes are pigmented.

Adrenal Glands.—Hyperplasia of the medulla. The cortex is fatty, and there is also serous vacuolation.

Thymus.—The lymphoid elements are atrophic. Hassal’s corpuscles are larger than normally.

Hypophysis.—Many fat and serous vacuoles are in the anterior lobe. There are numerous eosinophiles; no colloid formation.

Rabbit 44.—Female. August 21, 1911. Thyroidectomized. Weight, 245 gm. October 27, 1911. Died. Weight, 600 gm. Typical picture of cretin rabbit. Autopsy.—The subcutaneous tissues are pearly. 10.5 c.c. of clear peritoneal fluid was obtained which clotted in ten minutes. The pleural cavity is free. The pericardium is filled with fluid. The thymus is undersized. The aorta is opaque. The spleen is small, and the kidneys are normal. The medullas of the adrenals appear larger than normally in proportion to the cortex. The bone marrow is pale.

Microscopic Examination.

Hypophysis.—Large numbers of eosinophiles are found in the anterior lobe. Both the anterior and intermediary lobes are vacuolated.

Esophagus, Skin, Aorta, and Kidney.—All show blue staining, edematous connective tissue.

Thymus.—The lymphoid elements are atrophic, and the epithelial elements hypertrophic. Three parathyroid nodules occur in this section, and are similar in character to the parathyroid previously described.

The other tissues are of the same type as those previously described.

Rabbit 48.—Female. Typical cretin; age, 7 weeks. Of especial note is the occurrence of a parathyroid nodule in the thymus; also an edematous corium and subcutaneous tissue with a mucoid reaction.

Rabbits 67 (age, 10 days), 80 (age, 5 weeks), 101 (age, 6 weeks), 55, 57 (age, 4 months), and 90 (age, 2 months), need no especial description, as they all show the typical macroscopic and microscopic appearances.

Rabbit 96.—Male; age, 5 months. Typical cretin. Hematoxylin and eosin sections are typical.
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In order to ascertain the extent of fatty degeneration in the various tissues, tissues of rabbit 96 were stained with osmic acid. The microscopic analysis follows.

**Heart.**—Very fine black droplets were found along the fibrillae of the shell, but not in the central area of the fiber.

**Lungs.**—Fat was found only in a few large oval cells.

**Liver.**—Fat droplets are rather evenly distributed throughout all the liver cells. Around some of the portal veins were small accumulations of fat droplets in the connective tissue cells.

**Spleen.**—A small amount of fat is diffusely spread throughout the organ.

**Kidney.**—A small amount of fat is found in scattered areas only.

**Pancreas.**—Scattered granules are found throughout except in the islands of Langerhans.

**Testis.**—Black droplets were found mostly in the epithelial cells, yet some cells were free from fat. A slight amount of fat was found in the perivascular connective tissues, and in certain extratubular cells.

**Urinary Bladder.**—The epithelial cells appear swollen, yet clear, with no signs of fat. The connective tissue immediately below was rich in fat, while none was found in the deep edematous connective tissue and muscle layers.

**Intestine.**—There is no fat in the muscle or ganglia, but considerable fat is found at the bases of the epithelium.

**Adrenals.**—The cortical cells are intensely fatty. There is no fat in the medulla.

The following is a summary of the constant morphological changes in the various organs, which characterize cretin rabbits.

**Heart.**—Swelling of the muscle cells with degeneration of the central sarcostyles, leaving a shell of external fibrillae, which are degenerate in character.

**Liver.**—Fatty degeneration in the mid and central lobular zones, with often a great swelling of cells due to serous imbibition.

**Kidney.**—Fatty and granular degeneration and vacuolation of the cortical epithelium. Hydrotic imbibition in the epithelial cells of the collecting tubules and ducts of Bellini; similar changes, also, in the epithelium of the kidney pelvis and urinary bladder.

**Lungs.**—Congestion; atelectasis; bronchial collapse; and emphysema.

**Ovaries and Testes.**—Incompleteness or absence of development of the sex elements with degeneration of the germinal epithelium.

**Hypophysis and Parathyroid.**—Swelling of cells, together with serous and fatty vacuolation. No acinus or colloid formation.

**Pancreas.**—Hypertrophy and hyperplasia of the islands of Langerhans.

**Thymus.**—Atrophy of the lymphoid elements, and hypertrophy of the epithelial elements (Hassal's corpuscles).

**Muscle.**—Serous infiltration, atrophy, and fatty degeneration of the smooth and striated muscle.

**Bone Marrow.**—Fatty, inactive type, with leucogenetic centers in excess of the erythropoietic centers.
Adrenals.—Hypertrophy of medullas with plentiful chromophile substance; also excessively fatty cortices.

Body Cavities, Skin, and Connective Tissues.—Ascites; hydropericardium. Edema of the connective tissues generally is well marked in the true skin. This edema only occasionally gives a mucoid reaction with hematoxylin.

The degenerative changes in the myocardium are very pronounced. The individual cells are mostly somewhat swollen, and usually with but a single layer of external sarcostyles. The area of the undifferentiated cytoplasm, as described by MacCallum, is very small in the normal rabbit, and requires careful observation in order to be seen at all. In the heart cells of this series, the undifferentiated areas comprise a major part of the fiber. This may be due in part to a serous imbibition, associated with the central sarcostyle degeneration. The muscle in this condition cannot be otherwise than very weak, and forms a probable cause of the extreme dilatation and congestion of the lung vessels, and of the ascites and general tissue edema in the various organs. Although a similar degeneration of heart muscle of the rabbit is found as the result of other causes, yet in no case have I found such a general involvement of heart fibers as in these cretin rabbits. In other conditions, the degeneration is limited to small areas and borders, particularly those lining the cavities of the heart. Bensen, in studying the histology of thyroidectomized adult rabbits, and Kishi, in thyroidectomized cats and dogs, saw changes in the heart muscle, but laid no particular stress on such a condition. They found some granular degeneration, an increase in prominence in the longitudinal striation, with partial disappearance of the transverse striation. Bensen speaks of one case in which the fibrillae were spread apart as if by edema, and in which a few fibers were devoid of nuclei, thus leaving a clear space. I have not studied cardiac muscle changes in thyroidectomized adult rabbits, dogs, or cats, but from the findings of Bensen and of Kishi it is evident that relatively slight changes occur. In contrast with this, my results indicate a very marked increased sensibility of the heart of the young rabbit towards the deleterious effect of athyroidism.

To what extent the degenerative changes in the liver may be due to cardiac insufficiency is difficult to determine. The marked
swelling of the cells, with thin cytoplasm and prominent granules, might be referable to a serous imbibition following venous stagnation, and in this manner the fatty degeneration of the cells of the central and mid zones might be explained, yet both lesions might be attributed to disarrangement of the internal metabolic activity of the cell dependent upon the absence of the thyroid secretion. Bensen found in some of his series a "pflanzenzellenartiges Aussehen" of the liver cells, and this condition is also described by Gozzi. This is essentially the same as in the present series. Rosenblatt found hyperemia and small hemorrhages, and some parenchymatous degeneration; while Hofmeister could see no constant abnormality. Halsted found the liver of a myxedematous dog to be normal. Since Rosenblatt and Halsted both used the dog, their series may not be comparable to mine, yet it might well be true that their different liver findings were due to a less affected condition of the heart.

The most characteristic feature of the kidney is the signet ring vacuolation of the cells of the collecting tubules and ducts of Bellini, also in the transitional epithelium of the urinary tract. There is also a marked parenchymatous degeneration and vacuolation of the epithelium of the convoluted tubules, and hydropic imbibition or vacuolation in the glomerular tuft epithelium. Colloid-like granules are found in the epithelium of the convoluted tubules. Parenchymatous degeneration was found by Bensen, Blum, Haskovec, Rosenblatt, D'Amore, Falcone, and Gioffredi. Hofmeister concluded that the only constant change was the peculiar hydropic imbibition of the cells of the collecting tubules. He had not studied the transitional epithelium of the urinary tract.

The amount of thymus tissue varied considerably in the different individuals. The lymphoid elements were atrophic, while the epithelial elements, or Hassal's corpuscles, were hypertrophic. Hofmeister, Haushalter and Jeandelize, and Blumreich and Jacoby, all found atrophic thymus glands, but did not notice any increased prominence of the epithelial portion. Blumreich and Jacoby state that the thymus atrophied in all of their series, even in those that showed no cachexia; and further, in some instances, they could find no trace of the thymus. I have always been able to find the thymus
in the cretin rabbit, but often care had to be exercised in order not to miss it. It must be recalled in this connection that the young adult rabbit has quite a large persistent thymus, and consequently the atrophic types, found in athyroid rabbits, is a prominent feature of the autopsy. The cause of differing responses of the two elements towards thyroid loss is obscure.

Atrophy of the chief parenchyma of the genital glands is a constant feature. An early atrophy of the thymus, according to Paton, facilitates the development and maturation of the sex glands, but in athyroidism there is non-development and degeneration of all but the interstitial cells of Leydig in the male. The male animals frequently showed some sexual desire, which indicates a fairly healthy condition of the interstitial element. Atrophic sexual organs were obtained in experimental athyroidism by Moussu in 1892. Hofmeister, Langhans, Lancereaux, Lanz, Dolega, Abrikossoff, and Halsted, made similar observations in different species of animals, including man. Halsted, in reporting an autopsy of a myxedematous dog, states that not only was there complete absence of spermatogenesis, but also almost complete absence of the cells of Leydig. The thymus in this animal was somewhat atrophic. In the ovary in my series there is in general marked karyolysis in the smaller ova, while the larger ones show complete absence of a nucleus, and in fact usually degeneration of the cytoplasm. The germinal epithelium shows the vacuolation so prevalent in other organs.

With respect to changes in the external parathyroids, I find no evidences of transformation into thyroid characteristics. The cells are enlarged, but are also vacuolated by a serous material. No evidences of colloid or acinus formation have ever been seen. Pepere states that he has observed changes indicating increased parathyroid function, deeper staining cells, some tendency to form acini, with colloid apparently arising from degenerating cells within the encircling cells. He claims, however, that these signs are due to increased parathyroid function following a partial parathyroid tissue loss, and are not due to any vicarious assumption of a thyroid function. Certainly my series gives no support to the theory proposed by Gley, Baber, and Horsley, and later supported by Vin-
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cent and his associates. Gley and Nicolas, it will be recalled, later renounced the transformation theory. Vincent's criticism of such work is valid in so far as our operation is not a simple thyroidectomy, but also a removal of those internal parathyroids intimately associated anatomically with the thyroid lobes. Pepere called attention to the variability in size of these, that they were often extremely small, and hence the parathyroid loss associated with thyroidectomy in the rabbit removes a relatively small proportion of the whole parathyroid apparatus. It has been repeatedly shown that removal of one thyroid and the external parathyroid of the same side has no effect on the animal. In my operation, I have always preserved the external parathyroids intact, and have only observed cachexia thyropri...
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Rogowitsch in 1889, then confirmed by Stieda, Tizzoni and Centanni, Gley, and many others. Hofmeister, and also Alquier, considered the enlargement to be compensatory towards the thyroid loss. Schönemann, in making a study of the relation of the thyroid to hypophysis in human autopsy material, came to the conclusion that the hypophysis became enlarged due to degenerative causes rather than to compensation. Simpson and Hunter could find no iodin in the hypophysis of their thyroidectomized sheep, and concluded that if an iodized substance represented the essential secretion of the thyroid that the hypophysis could scarcely be considered to compensate by this means. Guerrini, Gemelli, de Coulon, Ponfick, and Pirone, believed with Schönemann that the hypophysial enlargement was not necessarily a vicarious compensation, but may be produced by many intoxications, such as diphtheria toxin, snake blood, and toxins from intestinal ligation. The hypophyses of my series are distinctly degenerate in character and would scarcely warrant an assumption of vicarious compensation, more than could equally well be ascribed to the enlarged liver cells.

The bone marrow is usually of an inactive, fatty type, with the erythrogenetic centers exceeded somewhat in numbers by the leucogenetic centers. Thus there is indicated a decreased production of erythrocytes. That there has been no excessive leucocyte demand is shown by fragmentation of leucocytes accumulated about the borders of the leucogenetic centers. The megalokaryocytes are degenerate in type. Esser, in 1907, found the bone marrow of the thyroidectomized rabbits to be fatty in type, with degenerating megalokaryocytes. He believes the bone marrow to be responsible for the anemia of hypothyroid animals.

The spleen of the cretin rabbit appeared small, though no measurements were taken. The histological picture is relatively constant. There is an excess of pigmented phagocytes indicative of an excessive erythrocyte destruction in the organism. Hyperplasia of the pulp and occasionally sclerosis may be referable to an early congestion which was present in some of the series. The congestion and pigmentation were observed by Bensen and by Gozzi. Zezas reported a vicarious hypertrophy, which was negativized by the work
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of Hofmeister and of de Guervain. Halsted found the spleen of the myxedematous dog to be normal.

The islands of Langerhans in the pancreas in this series were definitely hyperplastic and hypertrophic, and sharply defined, while the zymogenous tubule epithelium appeared normal. Most authors have failed to see any pancreatic changes in thyroidectomized animals, though Falta and Berterelli, according to Biedl, state an increase in size and number of the island cells in hypothyroidism. This condition has an interesting bearing on the question of increased sugar tolerance in cases of hypothyroidism. No evidences of any transition of zymogenous epithelium into islands of Langerhans could be seen. Both were sharply limited with no transitional types as described by Vincent.

The general condition of edema, ascites, and excessive pericardial fluid may be largely due to cardiac insufficiency, though it is not improbable that metabolic disturbances, as studied by Kottmann, may play an important rôle. The atelectasis and bronchial collapse seem explicable only on the assumption that the greatly widened pulmonary vessels following gradual cardiac failure have produced an increased intrathoracic pressure.

Both smooth and striated muscle show marked degeneration, the former giving rise to intestinal distension resulting in the pot belly symptom of all cretins; the latter explains the weakness of skeletal musculature.

SUMMARY.

In summarizing the findings of this paper it may be said that degenerative changes have been noted in practically every parenchymatous organ. Among these the most striking has been that of serous imbibition by the most active cells of these organs.

In regard to the changes in the glands of internal secretion, the findings corroborate the statements of Cushing in regard to hypophysectomy, that removal of one gland of internal secretion results in changes in all the other glands. In this case, degenerative changes predominate in the hypophysis, thymus, ovary, and testis, while hyperplasia is seen in the islands of Langerhans and the medullas of the adrenal glands.
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Finally, in the rabbit athyroidism is responsible for grave degenerative changes in practically all organs and tissues of the body, and many of the symptoms of cretinism have an anatomical basis in organic cellular changes.

In conclusion the author wishes to express his appreciation of the assistance of Professor C. H. Bunting, at whose suggestion the histological material was studied, and in whose laboratory the material was prepared. The author also takes pleasure in acknowledging to Professor A. S. Loevenhart many helpful suggestions.

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