EFFECTS OF INANITION UPON THE STRUCTURE OF THE THYROID AND PARATHYROID GLANDS OF THE ALBINO RAT

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INTRODUCTION

The thyroid gland presents an interesting and difficult biological problem. Although the morphology of the thyroid has been extensively studied, there are still many doubtful and unsettled questions concerning its development and its normal adult structure. Even more uncertainty exists concerning its physiological significance and its pathological changes. Some light may be thrown upon the various phases of this problem by a study of the changes produced in the thyroid gland by inanition.

In previous papers (Jackson '15 a, '15 b) it was shown that during inanition the various organs of the albino rat suffer very unequally in loss of weight, the loss also varying according to

the length and character of the inanition. In acute inanition of adult rats, with loss of about one-third in body weight, the thyroid gland had apparently lost but little if any in absolute weight; in chronic inanition of adults, the average apparent loss of the thyroid was about 22 per cent; while in young rats held at maintenance (constant body weight) by underfeeding for several weeks the average loss was about 24 per cent. In order to determine what histological changes are correlated with these changes in gross weight, material was preserved for further study. On account of its intimate association with the thyroid, the parathyroid gland was also included in this investigation. The results are presented in the present paper, which is the third of a series of studies upon the effects of inanition. The work is being carried on with the assistance of a special grant from the research fund of the Graduate School of the University of Minnesota.

MATERIAL AND METHODS

The material used included the thyroid (and included parathyroid) glands of the albino rat (*Mus norvegicus albinus*) from previous studies (Jackson '15 a, '15 b), together with some collected since. In all, more than 50 normal glands were sectioned and studied, varying in age from newborn to adult (15 months). These were chiefly controls from the same litters as those used for experiments (including several controls used in experiments by E. R. Hoskins and C. A. Stewart). In addition, I am indebted to Professor Bensley and Mr. Burgett, of the University of Chicago, Professor Addison, of the University of Pennsylvania, and Professor Evans, of the University of California, for material kindly furnished in order to investigate possible local variations in normal thyroid structure of the rat.

Of the animals subjected to inanition, the thyroid and parathyroid were obtained from 14 of the younger rats held at maintenance for various periods (chiefly beginning at 3 weeks and ending at 10 weeks of age). Of the adult rats, 6 glands were

studied from those subjected to acute inanition, and 3 from those with chronic inanition.

The material was obtained at the autopsy held immediately after the animals were killed, and was fixed chiefly in Zenker's fluid, 12 to 24 hours. In a few cases formalin or Flemming's fluid was used, but the results were less satisfactory.

The glands were embedded in paraffin, and cut at 5 micra (occasionally 7 to 10 micra) in thickness. In the great majority of cases, the glands were cut and mounted in complete serial sections. This was found to be important, not only to make certain of including the parathyroids, but also because the structure frequently varies in different parts of the thyroid and parathyroid glands.

The sections were stained in most cases with haematoxylin and eosin; in a few cases with iron-haematoxylin, safranin, Mallory's anilin-blue connective tissue stain, etc.

All of the drawings were made with a Zeiss 2 mm. 1.30 N. A. apochromatic objective and compensating ocular No. 6, with the aid of a camera lucida. A wheel-micrometer eyepiece was used for the measurements. It was the original intention to measure systematically a large number of cells and nuclei in the glands of the controls and of the animals subjected to inanition. On account of the great irregularity in the size and shape of cells and nuclei, however, it was found that the results, though of limited value, could not be obtained with sufficient accuracy to justify any very extensive series of observations. Therefore the number of measurements was restricted to that judged sufficient to give merely an approximation of the apparent average and range observed.

THE THYROID GLAND

The normal structure of the thyroid gland in the albino rat at various ages will first be considered. Then the changes found in the various types of inanition will be described and their significance discussed.

a. Normal structure of the thyroid gland

The general form and topography of the thyroid gland in the albino rat is shown in cross section in figure 1. Each lateral lobe presents the typical relations—convex external surface covered by the infrahyoid musculature; concave internal surface in contact with the lower larynx and upper trachea; and narrower posterior surface (or border) in relation with the oesophagus

Fig. 1 From a photograph (retouched) of a cross section of the thyroid gland in situ at the level of the isthmus, showing relations to infrahyoid musculature, uppermost trachea, oesophagus, etc. One parathyroid is visible, on the left side of the figure. From albino rat No. S 9.47, age 22 days, gross body-weight 25.5 grams. ($\times 28$.)

medially the carotid artery, etc., laterally. The isthmus is frequently a very thin somewhat fibrous band, almost invisible when the fresh gland is exposed in situ. It invariably contains thyroid follicles (contrary to Sobotta '15), although these may become scattered and more or less atrophied in adult rats.

The minute structure of the normal thyroid gland at 3 weeks (the age when the experiments began with the younger rats) is shown with slight magnification in figure 1, and under high power in figure 2. No attempt will be made to describe in detail the

minute structure of the gland, but some of the essential features especially affected by inanition will be considered briefly.

Fig. 2 A small portion of the thyroid gland shown in figure 1 (rat S 9.47, age 22 days) magnified to show the details of the normal histological structure. Several follicles containing colloid are shown. Follicular epithelium cuboidal; cytoplasm abundant and granular, with a few scattered vacuoles. Apparent origin of the colloid 'vacuoles' from the epithelial cells is shown in a few places. Four interfollicular epithelial cells are seen between the two lower follicles. Fibrous stroma scanty, with rich blood-vascular plexus. ($\times 750$.)

The follicles at this time are chiefly oval or rounded in outline and vary mostly from 20 to 70 micra in diameter. The larger follicles are rather infrequent and somewhat uniformly scattered, but are usually more frequent near the surface of the gland. Those shown in figure 2 are of average size.

The finer structure of the thyroid gland is shown in figure 2. The cells of the follicular epithelium are approximately cuboidal in form (in some cases low columnar; in others, especially in the larger peripheral follicles, somewhat flattened). In height, they range chiefly between 8 and 15 micra, the average being 10 to 12 micra. The inner and outer cell walls are sharply distinct; the intercellular boundaries are less distinct and sometimes absent.

The cytoplasm of the follicular cells (fig. 2) is filled with moderately fine granules, reddish violet in color (with Zenker fixation and haematoxylin-eosin stain). The granules are usually somewhat uniformly distributed. They are not densely packed, but are sometimes arranged so as to give an indefinite reticular form, apparently intermingled with small, clear vacuoles. Some of these vacuoles (though not all) may correspond to the minute fat droplets or granules described in the thyroid cells by Erdheim ('03) and Traina ('04). The cells present a fairly uniform appearance, and there is nothing to indicate any division into the 'chief' and 'colloid' cell types of Langendorff.

The nuclei of the follicular cells are spherical or slightly ovoidal (ellipsoidal) in form, the diameters varying from 4 to 7 micra, usually 5 or 6 micra. The nuclear membrane is distinct and stains deeply. There are usually one or two larger nucleoli (karyosomes) and several smaller granules; and a fine, paler nuclear network, often indistinct, with a very pale bluish, homogeneous nuclear background, corresponding to the nuclear sap (karyolymph). The nuclei shown in figure 2 are typical, though in the larger peripheral follicles with slightly flattened cells the nuclei may also be somewhat more flattened and slightly hyperchromatic. Cells in mitosis are relatively frequent, 5 having been noted in one entire cross-section of one lobe, and 6 or 8 in another.

The colloid (fig. 2) appears typical in form though somewhat variable in staining reactions. In some cases it fills the follicular cavity completely, in other cases it is retracted somewhat with either smooth or serrated margin. This retraction is probably an artefact in most cases, due to shrinkage produced by the reagents used. But I cannot agree with those investigators who explain the vacuoles (some of which are shown in figure 2) in a similar manner. These vacuoles are usually small (4 micra or less) and spherical in form, and are most frequent near the surface of the colloid. Occasionally they are found in intimate relation with the adjacent cells, from which they are apparently extruded, as shown in the follicle on the right in figure 2. They are probably connected in some way with the process of colloid formation, as described by Anderson ('94) and Müller ('96). Desquamated epithelial cells, which sometimes dissolve leaving clear vacuoles in the colloid in older rats, are extremely rare at this stage.

A variable amount of interfollicular epithelium appears, which cannot be distinguished from tangential sections of follicles, except in serial sections. In structure, these interstitial epithelial cells are similar to those of the follicles. A few appear in the lower part of figure 2.

The interfollicular connective tissue forms a delicate fibrous stroma (fig. 2), relatively small in amount, but containing a rich capillary plexus of blood-vessels. The nuclei visible are mostly of capillary endothelium. They are elongated or flattened in form, and stain somewhat deeply.

At 10 weeks (the age when the inanition experiments ended in most of the younger rats) the thyroid gland has normally undergone but slight changes, the structure being essentially the same as that just described at three weeks. Therefore no detailed figures are considered necessary. A photograph with low magnification is shown in figure 3, representing a cross section of one lateral lobe. The follicles have increased somewhat in size, the maximum diameter now reaching about 100 micra. The larger follicles are more frequent, and are sometimes rather uniformly distributed, as shown in figure 3, though very frequently

Fig. 3 From a photograph of one lobe of the thyroid gland from normal albino rat No. S 5.3, age 74 days, gross body-weight 172 grams. Parathyroid included. Compare with figures 4, 5 and 6, representing thyroids in rats of the same age, but held at maintenance from age of 3 weeks. ($\times 28$.)

Fig. 4 From a photograph of one lobe of the thyroid gland from albino rat No. S 11.63, age 72 days, gross body-weight 23.8 grams (held at maintenance from age of 3 weeks). Follicles much larger at periphery. Some extra-capsular tissue is included. Parathyroid relatively large. ($\times 28$.)

there is a distinct tendency to larger follicles in the superficial layers.

In finer structure, the thyroid at 10 weeks is very similar to that shown at 3 weeks (fig. 2). The height of the follicular cells varies considerably, however. While the maximum is about the same as at 3 weeks, the average (about 8 to 10 micra) is somewhat lower. In other words, the cells are usually more flattened, especially toward the periphery of the gland. In the larger surface follicles, the cells are usually distinctly flattened, 6 micra or less in height. The nuclei in these cells are also correspondingly flattened, their diameters averaging 4×6 micra. The nuclei in general are similar to those at 3 weeks in size and structure, usually nearly spherical in form, and averaging about 6 micra in diameter. Mitosis is very much less frequent in the cells of the thyroid at 10 weeks than was found in the gland at 3 weeks.

While the typical normal structure of the thyroid cells at 10 weeks is like that at 3 weeks (fig. 2), cells of abnormal appearance are also found. These atypical forms vary from slight modifications up to marked cellular degenerations, and should be carefully noted in order to avoid confusion with the changes during inanition to be described later.

The flattening of the epithelium in the larger peripheral follicles is almost constant, though variable in extent. The flattened nuclei are hyperchromatic in type, and often present a more or less deeply-staining, homogeneous background, which may obscure or obliterate the nuclear network and granules. The cytoplasm is reduced in amount, more deeply-staining, and often somewhat homogeneous in appearance. This type of cell occurs so constantly in the peripheral follicles (and occasionally elsewhere) that it can hardly be considered abnormal. I inter-

Fig. 5 From a photograph of one lobe of the thyroid gland from albino rat No. S 5.10, age 67 days, gross body-weight 22.7 grams (held at maintenance from age of 3 weeks). Gland small, with relative increase of stroma. Parathyroid included. ($\times 28$.)

Fig. 6 From a photograph of both lobes and a portion of the isthmus of the thyroid gland from albino rat No. S 11.64, age 73 days, gross body-weight 24.2 grams (held at maintenance from age of 3 weeks). Follicles larger at periphery but irregular, many degenerated. Parathyroids relatively large. ($\times 28$.)

pret it as an atrophic type, due perhaps largely to the pressure on the gland from adjacent organs. Although these follicles are filled with dense, deeply-staining colloid, it is unlikely that the flattening is due entirely to consequent endofollicular pressure, as follicles are sometimes seen in which the epithelium on the external surface is much more flattened than that on the inner aspect of the follicle. The so-called 'colloid' cells of Langendorff (frequently described by various authors) probably belong to this atrophic type, and have no specific functional significance.

In addition to these peripheral flattened atrophic cells, mention must be made of more advanced types of degeneration, although the latter appear much less frequent in the young rat at 10 weeks than in older animals. These degenerative cells may occur in any part of the gland, either singly or involving an entire follicle (occasionally a regional group of follicles). The degenerating cells may remain in the follicular wall or may be desquamated into the follicular cavity. In rare cases the desquamated epithelium may replace the colloid with an irregular mass of cells in various stages of degeneration.

In the degenerating cells, the cytoplasm loses its typical light granular structure and becomes vacuolated and reticular in appearance, later disintegrating into irregular, usually deeply-staining (eosinophile) masses. The nucleus may be hypochromatic (karyolytic) in type, but more frequently presents various grades of pycnosis (rarely karyorrhexis), especially in the desquamated cells.

As to the frequency with which these degenerative types of cell occur in the thyroid of (apparently) normal rats at 10 weeks, it may be stated that of 9 glands carefully examined in serial sections, one showed rather extensive degeneration, one a well marked area (much less extensive), and four showed traces or small areas in early stages of degeneration. Thus in a majority of the glands, at least slight traces of degeneration could be found, even in normal, apparently perfectly healthy animals.

In older rats (from 3 to 15 months of age), the normal structure of the thyroid gland is essentially similar to that described for the younger rats. The follicles average slightly larger, the

maximum sometimes reaching 150 micra, the largest follicles being frequently found at the periphery of the gland. While cubical cells still occur to a variable extent, the average cell is somewhat more flattened than at 10 weeks, especially in the larger peripheral follicles. The colloid is variable in appearance. Occasionally the follicular content may be clear and unstainable. The stroma remains as previously described.

The most striking difference in the thyroid of the older rats is found in increasing prevalence of the degenerative process already described as appearing at 10 weeks. In the older control rats it was found not only more frequently, but more pronounced in character. In extreme cases, the follicles in some regions (see fig. 10) are entirely obliterated, being replaced by masses of epithelial cells with irregularly disintegrated cytoplasm and nuclei in various stages of pycnosis or karyorrhexis. Among 20 glands from apparently normal older rats, only 3 thyroids appeared entirely normal; 6 showed slight degeneration, 5 were moderately involved, while in 6 the degeneration was extensive, involving the larger portion of the gland. The significance of this appearance of degeneration in normal animals will be discussed later.

b. Structure of thyroid gland in young rats held at maintenance

The appearance of the thyroid gland in young rats held at constant body-weight from 3 to 10 weeks of age is shown under low magnification in figures 4, 5 and 6, and more highly magnified in figures 7, 8 and 9. The follicles in general appear in average size smaller than the normal at 10 weeks, although it is somewhat difficult to make exact comparisons, on account of the irregularity in their size. The maximum diameter found in 9 normal glands was about 100 micra, whereas in 14 maintenance rats it was 85-90 micra. The average in both cases was of course much lower, as follicles are found of all sizes down to those with only a minute cavity. Although in the maintenance rats at 10 weeks a few follicles are larger than found in the normal rat at the age of 3 weeks (where the maximum was 70 micra), it is doubtful whether the average follicle is any larger. It is probably slightly smaller.

In size, the epithelial cells of the thyroid follicles in the young rats held at maintenance are variable but distinctly smaller than normal. Even the largest cells found rarely reach the average

Fig. 7 A portion of the same thyroid gland shown in figure 4 (rat No. 11.63, maintenance from 21 to 72 days of age), magnified to show details of histological structure. The area represented shows the hypochromatic (incipient karyolytic) type of nuclear structure, which is relatively infrequent. Cells reduced in average height (cf. fig. 2). Cytoplasm reduced in amount and vacuolated in structure. Stroma here normal. ($\times 750$.)

normal height (8–10 micra) at corresponding age. The average height in the maintenance rats is about 6 to 7 micra. Since the

Fig. 8 A portion of the same thyroid gland shown in figure 5 (rat No. S 5.10, maintenance from 21 to 67 days of age), magnified to show details of histological structure. This represents the hyperchromatic (various stages of karyopycnosis) type of structure, which is typical. Follicular cells usually greatly reduced in size. Cytoplasm much reduced in amount and markedly vacuolated ('hydropic degeneration'). Colloid variable in appearance. Interfollicular stroma relatively much increased in volume, due to infiltration of clear ground substance. ($\times 750$.)

whole follicle is but slightly below the normal size, it follows that the cells are more reduced in height than in width. In some glands, the follicular epithelium is very strikingly flattened throughout the entire gland, in no place exceeding 4 or 5 micra in height. Such a condition is never found in the normal gland.

Fig. 9 A portion of the same thyroid gland shown in figure 6 (rat No. 11.64, maintenance from 21 to 73 days of age), magnified to show details of histological structure. This area represents advanced stages of follicular degeneration. Cells in various stages of degeneration and disintegration. Tendency to desquamation with destruction of colloid and obliteration of follicular cavity. Some nuclei appear karyolytic, although karyopenosis predominates, and karyorrhexis frequently appears. ($\times 750$.)

In the larger peripheral follicles, in which the epithelium is normally flattened, the change is usually not so apparent in the maintenance rats. Even here, however, there is a further flattening of the epithelial cells, which frequently present an endothelial-like appearance, with a height of only 2 or 3 micra.

The cytoplasm of the thyroid epithelium in the maintenance rats has undergone marked changes (figs. 7, 8, 9). In comparison with the normal (fig. 2), it appears that the amount has been greatly reduced, the decrease in the size of the cell being due very largely to loss of cytoplasm.

The cytoplasm is also greatly changed in structure, having apparently undergone a 'hydropic degeneration.' The normal granular appearance of the cells (fig. 2) has been replaced very largely by a distinct reticular appearance (figs. 7 and 8). This appears to be due to a coarse vacuolization of the cytoplasm, a condition rarely found in the normal gland. The vacuolization is especially marked in the few larger cells which have retained more cytoplasm than usual. Occasionally the vacuoles coalesce to form perfectly clear perinuclear areas (see upper part of fig. 8). These clear areas and vacuoles probably represent a watery fluid replacing the normal granular substance, which has been removed and consumed as a result of the inanition.

Where the cytoplasm is very greatly reduced in amount (as in the larger peripheral follicles), the vacuoles may be finer or absent, and the cytoplasm here presents a denser, more deeply-staining (eosinophile), often homogeneous appearance ('colloid' type). In the case of cells in advanced stages of degeneration (which appear much more frequent and more pronounced than in the normal at this age), the cytoplasm is more or less disintegrated and extremely varied in appearance (fig. 9). It usually presents an irregular, deeply-staining (eosinophile), coarsely granular mass, which, especially in the desquamated cells, becomes fragmented and is gradually absorbed, frequently leaving behind the naked, pycnotic nuclei (fig. 9). The cell walls are often distinct in the less modified epithelium, but usually indistinct or lost in the cells markedly degenerated.

The nuclei, generally speaking, appear somewhat more resistant to inanition than does the cytoplasm. In form and size, there appears to be comparatively little change in many of the thyroid nuclei in rats held at maintenance from 3 to 10 weeks of age. The average diameter found in the nucleus of the more nearly cubical cells is between 5 and 6 micra, while the normal at corresponding age is only about 6 micra. It is therefore evident that the nuclear decrease in volume is relatively small. (A decrease of even 10 per cent in the nuclear diameter would correspond to a loss of about 27 per cent in volume, however.) In the more flattened cells (which, as we have seen, usually include the majority), the nucleus is also usually correspondingly flattened, with some loss in volume. Even in the flattened cells, however, the nuclear loss is apparently relatively much less than the cytoplasmic loss in volume.

Although the loss in volume of the nucleus in the thyroid of maintenance rats is relatively small, the structure is usually distinctly modified. Nuclei of the typical normal appearance (as in fig. 2) are rare. The modifications found are varied, but may be classified in two groups—hypochromatic and hyperchromatic.

The hypochromatic type is comparatively rare. In 14 cases of maintenance rats, it appeared extensively but once (shown in fig. 7), and in 3 other cases more or less frequently in scattered cells. The hypochromatic nuclei (fig. 7) usually appear normal in size, or even slightly swollen. They are very light and vesicular in appearance. The nuclear membrane is thin, but sharp and clear; the nuclear network and granules faint and indistinct. The interior of the nucleus is filled with a clear nuclear sap (karyolymph), which is nearly colorless, or with a very pale blue homogeneous tint. In exceptional cases these hypochromatic nuclei apparently undergo complete karyolysis, and disappear without preceding change in form or size.

The hyperchromatic form of nucleus on the other hand, is typical. In the 14 cases of maintenance rats, it appeared more or less extensively in thyroid of all (even in the one case in which the hypochromatic type predominated). Apparently the earli-

est stage (or at any rate that departing least from the normal type) consists in a mere thickening of the nuclear membrane ("nuclear wall hyperchromatosis") or an increase in the number and size of the nuclear chromatic granules, so that as a whole the nucleus appears darker and more deeply-staining than usual. This form appears normally in the more flattened cells of the larger peripheral follicles, and in the maintenance rats occurs more or less frequently throughout the gland, associated with the shrinkage and flattening of the cells (especially where the nucleus is also flattened).

Associated with or following the nuclear hyperchromatosis just described (in some cases perhaps independently thereof) is found a deepening coloration of the homogeneous nuclear background, which gives the appearance shown in figure 8. This appearance of incipient pycnosis is very characteristic and represents the predominant type of nuclear change observed. Apparently the process involves a progressive dissolution of the basic chromatin masses, which are probably dissolved in the nuclear sap. Various stages occur. The earliest show merely a slight darkening of the homogeneous background, which gradually increases until the nuclear net and karyosomes are obscured and finally disappear (figs. 8 and 9). In size, the nucleus at first shows no marked change (beyond perhaps a slight preliminary shrinkage), but as the process continues the nucleus usually decreases greatly in size. In the typical rounded, homogeneous, dense pycnotic nuclei, the diameter rarely exceeds 4 micra, which represents a tremendous shrinkage. When this stage is reached, the nuclei may apparently persist for a long time without further change, even though the cytoplasm has been reduced to a vestige or entirely removed (as, for example, in the mass of nuclei on the right in figure 9). In many cases of advanced cellular degeneration, however, the pycnotic nuclei become irregular in form and may later undergo karyorrhexis, breaking up into fragments which eventually through karyolysis are dissolved and disappear. Some of these extreme stages of karyorrhexis are shown in figure 9.

In no case was cell-division, either mitotic or amitotic, observed in the thyroid gland of the young rats held at maintenance for several weeks.

The colloid in the thyroid of the maintenance rats is usually nearly normal in appearance (figs. 7, 8), excepting those follicles with advanced degeneration of the epithelium. In these (fig. 9), especially where the epithelial cells are desquamated, the colloid becomes more or less granular and fragmented, finally appearing as irregular masses among the cellular debris or disappearing altogether. The follicles in advanced stages of degeneration are often very irregular in form.

The interfollicular (interstitial) epithelial cells (shown in figures 7 and 8), appear to undergo changes very similar to those in the epithelium of adjacent follicles.

The interstitial connective tissue or stroma of the thyroid in maintenance rats may be nearly normal in amount and structure (as in figure 7), but is frequently increased. This increase is apparently due to an infiltration of clear ground-substance, which in extreme cases gives a very pronounced swollen, 'water-logged' appearance (figs. 5, 8). It is evident that in such a case the weight of the gland might remain normal, even with a marked atrophy of the parenchyma. The fibers adjacent to the follicles may form a denser layer, resembling a basement membrane (fig. 8). The nuclei of the connective tissue cells become shrunken and pycnotic. The vessels may appear nearly normal, although degenerated areas sometimes appear hyperemic.

c. Structure of the thyroid gland in adult rats after acute or chronic inanition

In 6 adult rats whose thyroid was studied the body weight had been reduced 29 to 38 per cent by acute inanition (water but no food) for 8 to 11 days; and in 3 adults the amount of food had been reduced so there was a gradual loss of 33 to 37 per cent in body weight during the chronic inanition period of 5 weeks. The thyroid gland averaged about 0.039 g. (0.24 per cent of the net body weight) in both series, which (compared with controls)

indicates little or no loss in absolute weight during inanition. There was found, however, in a larger series of observations an apparent loss of about 22 per cent in the weight of the thyroid gland during chronic inanition (Jackson '15 a).

In the series studied, the structure of the thyroid varied considerably, but on the whole the changes appear to be essentially similar to those already described for the younger rats held at maintenance (really in a condition of chronic inanition).

No constant difference was apparent between the adults with acute and those with chronic inanition. The thyroid follicles are usually but little if any reduced in size. The colloid usually appears nearly normal in amount and structure, and colloid makes up a large portion of the gland. The cells are frequently cuboidal in the central portion of the gland, but on the average somewhat reduced in height. Also, especially in the few cells not reduced in size, the cytoplasm usually assumes a pronounced coarsely vacuolar structure ('hydropic degeneration'), which probably signifies an increase in water with a reduction in the amount of living substance. The nuclei frequently appear but slightly reduced in size, and show a marked tendency to hyperchromatosis (various stages of pycnosis), more rarely hypochromatosis (karyolysis). In the frequent advanced stages of degeneration, desquamation of the follicular epithelium with obliteration of the follicles occurs as previously described in the normal adult gland (fig. 10). Since these degenerative changes occur also in the normal (control) rats, they could not be considered a result of the experiment, except that they usually appear much more extensive and pronounced in the rats subjected to inanition. In the younger rats, however, as we have seen, the degenerative changes occur much less frequently in the normal rats, and the younger animals are therefore more satisfactory for the experiment.

The stroma of the thyroid in adult rats as a rule shows little change during inanition, although there is some tendency to increase in amount, with slight edema (less marked than in the younger rats). There is also frequently a slight hyperemia, especially in degenerating areas. The increase in the volume of

the interstitial substance is probably sufficient in most cases to offset the decrease in volume of parenchyma, so that if the colloid remains approximately normal in amount, the stationary absolute weight of the adult thyroid gland during inanition is explained. The greater tendency to loss in weight of the thyroid during chronic inanition and in younger rats is probably due to greater atrophy of the parenchyma, and in some cases to loss of colloid.

Fig. 10 From a photograph of a portion of the thyroid gland of a normal adult rat (No. S 14 x, gross body-weight 252 grams), moderately magnified to show typical 'spontaneous' degeneration of the follicles. Nuclei in various stages of pycnosis. Tendency to desquamation of epithelium with obliteration of the follicular cavity. ($\times 350$.)

d. Discussion and conclusions

The question of the extent and significance of the normal variation in the thyroid, with especial reference to the so-called degenerative changes, will be considered first, followed by a discussion of the specific changes produced by inanition.

The extreme variability in the form and structure of the follicular epithelium was observed by many of the earlier investigators. These variations were usually ascribed to age differences or to functional changes. The frequent presence of cells

in the follicular cavity was also noted, and the question as to whether the colloid is derived from these desquamated cells or is secreted by the epithelium of the follicular wall was long disputed.

Langendorff ('89), in addition to his well-known 'chief' and 'colloid' cell types, also recognized a retrogressive, degenerative type, which however he did not clearly differentiate from his 'colloid' type (except in theory). Langendorff's results were confirmed by Bozzi ('95), Schmid ('96) and others.

On the other hand, Hürthle ('94) claimed that colloid is formed both by cells of the 'colloid' type and by transformation of desquamated epithelium. Anderson ('94) Müller ('96) and others have opposed the theory that cells of Langendorff's 'colloid' type represent functionally active cells, considering them either functionally exhausted or atrophic, degenerative types, which appears to be the most reasonable interpretation.

De Quervain ('04) made an extensive study of thyroid pathology in man and animals (experiments on dogs and monkeys). From his results, the following conclusions are quoted concerning desquamation and degeneration of the follicular epithelium:

(p. 139) Wir halten also als Ergebnis dieser 3 Versuchsgruppen fest, dass sich sowohl durch Toxinwirkung, wie auch durch Erzeugung von hochgradigen Zirkulationsstörungen an der Schilddrüse histologische Veränderungen erzeugen lassen, die wesentlich durch Wucherung, Desquamation und Degeneration der Epithelzellen gekennzeichnet sind.

(p. 142) Wir kommen zu dem Verhalten der Epithelzellen, das uns vor allem interessiert. Die Reaktion derselben auf jeglichen Reiz besteht hauptsächlich in Desquamation. Wenn wir in diesem Abschnitte von Desquamation reden, so verstehen wir darunter die Abstossung von Zellen mit nachfolgendem Ersatz, und nicht etwa nur die postmortale Ablösung der Epithelzellen von der Bläschenwand. Auch die vitale Ablösung der Zellen ohne Ersatz infolge von Nekrose wird uns nur ausnahmsweise beschäftigen. Die Abstossung von Epithelzellen ist an sich ein normaler Vorgang, und lässt sich an völlig gesunden Schilddrüsen nachweisen; doch ist die normale Abstossung eine sehr beschränkte und man wird nur ab und zu in einem Bläschen eine oder einige Zellen bzw. Kerne in Kolloid schwimmen sehen.

Similar retrogressive changes (frequently considered normal) have been described in the thyroid gland in children, and even

in newborn and late fetuses (Zielinska '94, Elkes '03, Hesselberg '10, Isenschmid '10, Gleim '12).

Watson ('09) in 40 wild rats (species not stated) weighing 60 to 370 grams found wide variations in the thyroid structure, which he described under four types. His first type presents large colloid-filled follicles with flattened cells and darkly-stained nuclei. His second type shows smaller follicles with small cuboidal cells with relatively little cytoplasm and with rounded nuclei (appearing deeply-stained in his figure 2 A). In type 3, the follicles are small, cells large with abundant cytoplasm, and colloid faintly-staining. In type 4, the follicle cells are detached and distorted, with pycnotic nuclei and cytoplasm of variable amount and appearance. Types 1 and 2 (with intermediate forms) predominated in 31 of the 40 glands, type 3 in 5 and type 4 in 4 cases.

Watson concluded that these variations found in thyroid structure "have been induced by dietetic or other factors in the animal's environment." He thought that they did not represent different stages of functional glandular activity (related to digestion), since they were not correlated with the nature of the stomach contents. He does not mention the possibility of inanition, which according to my results might be the cause of his types 1 and 2. The fact that type 1 was found in animals with both full and empty stomachs does not disprove this, as the history previous to capture is unknown and the length of time the animals were fed is not stated. Type 3 is obviously that usually described as normal and type 4 corresponds to the degenerative type which I have found frequently in apparently normal animals.

In previous work, Watson ('05) had studied the effect of a meat diet upon the thyroid gland of 12 tame rats (11 were 6 to 12 weeks of age, 1 adult) with 8 controls. The experiment lasted 6 weeks to 4 months; and the meat-fed animals were usually retarded in body weight. Ten of the 12 showed marked changes in the thyroid, including congestion, epithelial proliferation of the follicles and degeneration of the colloid. (Similar results in meat-fed rats were obtained by Tanberg, cited by Biedl '13.)

In a later paper, Watson ('07 a) studied the thyroid in 20 wild rats, 10 of which were killed immediately after capture and 10 fed bread and milk for 10 weeks. The former showed large colloid-filled follicles with flattened epithelium; the latter had smaller follicles, with little colloid and cubical epithelium. Waters ascribes the change to the difference in diet; but here, as also in his meat-fed rats, it is difficult to exclude the factor of inanition (inadequate nutrition). He also failed to note that the degeneration may occur apparently spontaneously. In another paper Watson ('07 b) finds in young rats fed on oatmeal diet for several weeks a marked enlargement of the thyroid (0.078 per cent of the body weight as compared with 0.029 per cent in controls). In some cases, the thyroid epithelial cells were swollen and detached.

Rebello and DaCosta ('10) describe the thyroid of the normal rabbit as variable in structure with the occurrence of epithelial desquamation and degeneration, resulting in obliteration of the follicles in a manner very similar to that described above for the rat. They consider this a normal physiological process following functional activity. However they find the degeneration markedly increased by the injection of thyroid-proteid extracts. They also observed similar degenerated areas in the thyroid of a normal young dog.

Douglas ('15) in an extensive study of the effects of various diets upon the thyroid of pigeons, chicks and rats, described four types of structure, somewhat similar to those of Watson. He concludes that:

The histological appearances do not represent different stages of secretion, comparable to those of secreting glands engaged in the process of digestion. Under similar conditions and in animals fed on similar diets, the appearances in the thyroid differ very markedly. One observes all stages from the type with large vesicles, full of colloid with flattened cells, to that of a thyroid with no colloid and columnar shaped cells. Also the thyroid may be wholly or partly disintegrated. The variation in appearance of the thyroid seems to depend to some extent on the nutrition, and is thus only in this way dependent on the diet.

Out of 31 rats (species not stated) with "ordinary laboratory diet of bread" Douglas found the degenerative type of thyroid

only once, though it occurred frequently in pigeons and chicks. It occurred very frequently (8 of 11 cases), however, among rats fed various food mixtures with fat. The normal rats usually presented thyroid follicles with cubical cells and a moderate amount of colloid.

The variability in the structure of the thyroid gland and its physiological and pathological relations have been discussed by Marine and Lenhart ('09 a, '09 b, '11 a, '11b, '11 c) in a series of papers. On the basis of an extensive investigation of the human and animal (dog, sheep, ox, pig, etc.) thyroid, they distinguish as 'physiological' the following: (1) normal resting gland, with low cuboidal epithelium; (2) hyperactive stage, with hyperemia, cells becoming hyperplastic and columnar, colloid disappearing; (3) colloidal stage (of recovery), in which conditions again return to (1) with abundant colloid. If hyperactivity continues without rest, however, colloid disappears and the cells die of exhaustion, becoming progressively degenerated and desquamated with varied degrees of disintegration. The nuclei in this case are described as enlarged, often hyperchromatic, and quite variable in appearance. Similar desquamation and degeneration of the follicular epithelium is described in normal senile atrophy. The flattened type of epithelium, indicating a minimum functional activity, may be experimentally produced by administration of iodine in the diet; whereas a diet without iodine induces the columnar, hyperactive type of thyroid cells.

The variability in structure due to the extremely sensitive nature of the thyroid gland is emphasized by Marine and Lenhart ('11 c) as follows:

It has long been recognized and frequently emphasized by us that the thyroid tissue is extremely labile—reacting quickly to relatively slight physiological variations in the body metabolism, and for this reason may show even daily histological changes within narrow limits.

Marine ('15) also notes that thyroid glands undergo autolysis in a few hours after removal from the body, especially if kept near the body temperature, resulting in desquamation of the alveolar epithelium.

In a recent communication in reply to a letter of inquiry by the author, Dr. Marine states that he has frequently observed the so-called degenerative changes in the thyroid of the rat and other animals, and comments as follows:

I personally consider this change as a kind of autolysis. Autolysis in the thyroid is perhaps more easily recognized than in any other organ of the body because of its simple architecture. The change of which you speak consists of a desquamation of the alveolar cells and a breaking up of the cell membrane, giving a ragged appearance to the free border of the cells. This is always more marked in the slightly hyperplastic stages. Much has been made of this by various experimenters in an attempt to bring it into relation with the specific experiments that they were studying. It is of too general occurrence to have so varied a significance. The rat and the chick we have found to show these changes most frequently. One sees it in all chicks or rats that are autopsied some hours after death and even in rats sacrificed and autopsied at once, as all ours have been just for the purpose of eliminating this autolysis. I also think that formalin fixation is favorable for its development, as one rarely sees it in strictly fresh thyroids that have been fixed with metallic salts. In human thyroid pathology, as you are aware, this change has been described in almost every paper and in connection with the Basedow syndrome. Most writers who have studied the human thyroid have attempted to ascribe some peculiar toxic value to it. This is wrong. It is present in the cretin thyroid or in any active hyperplastic thyroid as well. In conclusion, therefore, I believe that this change is quite common in rats and fowl thyroids generally, and is of frequent occurrence in all thyroids unless the special precaution is taken of obtaining the tissues strictly fresh and fixing them in solutions other than formalin. I do not think it is any more common in starvation experiments than in other groups.

It might also be added that glands which have not been placed promptly in the fixative, and in which the process of post mortem autolysis has begun, sometimes show considerable differences in appearance at different depths from the surface. The fixation is better in the superficial layers than in the deeper strata which require a longer time for penetration.

In order to compare the structure of the thyroid gland, and especially the occurrence of degeneration, in the rats used by me with those elsewhere, I have obtained material from various localities. Professor Addison, of the University of Pennsylvania, kindly furnished mounted specimens of the thyroid from 3 nor-

mal albino rats. In a young rat (121 days), the structure was found nearly normal, the epithelial nuclei rarely showing incipient pycnosis. In 2 older rats, however, (200 and 452 days), there was found a considerable amount of epithelium showing desquamation and typical degenerative changes. In the thyroid of a gray rat (said to be a hybrid gray-albino) sent by Professor Evans, of the University of California, the structure was found nearly normal, but a few areas showed typical degeneration with partial desquamation of the epithelium.

Through the courtesy of Professor Bensley and Mr. Burgett, I obtained mounted specimens from 8 thyroids of normal albino rats (body weight 117 g. to 287 g.) from the University of Chicago laboratories. Of the 8 glands, 2 showed extensive follicular degeneration, 1 moderately extensive and 2 very small areas of slight degeneration. Only 3 appeared perfectly normal throughout.

Concerning the degenerative appearances found in the thyroid gland, Dr. Bensley writes:

There are two circumstances which should be borne in mind in connection with these changes in the thyroid gland, which frequently, I think, are responsible for similar changes in tissues which were normal to start with, namely: drying of the surface of the gland when adequate care is not taken in transferring to weighing bottles; and pinching with forceps in the process of extraction. The latter frequently initiates a rapid change in the cell which is marked by acid reaction to indicators, and by greater affinity for basic stains in the fixed preparation, with loss of characteristic structure by the nucleus.

In connection with the suggestion by Dr. Bensley of the importance of traumatic injury during the removal of the organ in producing degenerative changes, the observations of Sutherland ('15) upon pycnotic changes in nuclei of the spinal cord near the seat of injury may be cited.

From the foregoing, it appears that the characteristic follicular degeneration of the thyroid appears to a variable extent in apparently normal rats, both wild and albino, in widely separated localities.

Summing up the literature cited, together with my own observations, we may conclude that the thyroid gland shows an

unusual amount of normal variability in histological structure, doubtless due at least in part to functional stages which are as yet imperfectly understood. Furthermore, on account of the extreme sensitiveness of the thyroid, it reacts strongly to various influences by changes which lie on the border-line between normal and pathological. So-called degenerative conditions (desquamation and degeneration of epithelium) appear to a limited extent even in the thyroids of normal animals (including man), although these conditions probably have no physiological significance. Under various abnormal conditions, these retrogressive changes appear to be increased in extent and intensity.

Having reviewed the variable structure of the thyroid, we may now consider briefly the specific effects of inanition, as found by the few investigators who have studied the histological changes.

Barbèra ('02) studied the effects of acute inanition upon the thyroid gland in 3 rabbits and 1 dog, with controls of the same sex and from the same mother. The rabbits were starved 7 to 11 days, and the dog 21 days, with loss of about 30 per cent in body weight in each case. No data are given as to weight of the gland. No measurements of the entire cells are stated, but they were found reduced in size, the loss in the cytoplasm being greater than in the nucleus. The average of a large number of measurements of the nuclear diameters showed in the rabbit 5.73×4.99 micra in the controls, and 5.75×3.84 in the starved animals. This would indicate a reduction in size with relative elongation of the nuclei. This elongation of the nucleus was not found in the dog, however, where the average of 5.11×4.62 micra in the controls was reduced to 4.44×4.28 micra in the starved. The intercellular substance was also found reduced in amount, but colloid formation appeared to continue normally (hence no symptoms of hypothyroidism).

As above stated, I have likewise found in the rat thyroid during inanition a slight reduction in the size of the nucleus, which is usually much less marked than the decrease in cytoplasm. I find the shape of the nucleus dependent upon the form of the cell; in cases where the cell becomes flattened, the nucleus becomes correspondingly elongated, but otherwise it usually re-

tains its spherical or ovoidal (ellipsoidal) form. Morgulis ('11) found a tendency to relative elongation in the nuclei of various organs in *Diemyscylus* during starvation, but not in the liver and pancreas of the albino rat.

Traina ('04) finds in the thyroid of the rabbit during inanition a decrease of about 30 per cent in the volume of the cells, the loss being relatively greater in the cytoplasm than in the nucleus. The cells lose more in height than in breadth; the nucleus remains distinct and regular in outline. The fatty granules (previously described in the thyroid by Erdheim '03) remain in the atrophic cells unchanged in position, number, form and size.

Missiroli ('11) in rabbits finds the thyroid structure correlated with the stage of digestion present. When food is withheld, the colloid is no longer eliminated but accumulates and distends the follicles. In some cases of prolonged fasting, the colloid may undergo 'fatty degeneration.' In advanced stages of inanition, nuclei and protoplasm undergo atrophy, and the interstitial (connective) tissue appears increased. On refeeding, the colloid accumulated in the follicles is rapidly eliminated.

Mrs. Thompson ('11) states that:

In a dog which had been subjected to a few days' inanition, the thyroid (hardened in strong Flemming's fluid) appears very different from the normal. The cells appear swollen rather than proliferated, and in some cases vesicles are filled with cells. The vesicles are shrunk so as to assume various shapes, and much intervesicular material appears. The general appearance is as if the gland had been roughly squeezed, so that the vesicles are any shape but spherical. The change wrought by inanition seems to make the structure of the gland tend towards that of the parathyroid.

It is doubtful to what extent the changes described by Mrs. Thompson were actually due to inanition, since the inanition period was relatively short (for a dog) and the normal variation in structure is uncertain. She describes a similar appearance in the thyroid of a cereal-fed dog, while that of a meat-fed dog was normal.

In general, therefore, we find that the observations upon the structure of the thyroid during inanition, including those of pre-

vious observers and my own, while differing in various minor details, agree in the main. The epithelium of the thyroid follicles apparently undergoes at first a simple atrophy, which affects the cytoplasm more than the nucleus. The cells thus become reduced in height, with relatively large nuclei. In advanced stages of inanition, degenerative phenomena (found also to a limited extent even in the normal gland) become increasingly evident. The follicular cells may remain in situ, but usually are desquamated, replacing the colloid (which otherwise remains nearly normal). The cytoplasm, typically vacuolated in the earlier stages, may become collapsed, deeply-staining and more or less homogeneous ('colloid' type) in appearance, or may disintegrate, forming an irregular granular mass. The nucleus usually becomes hyperchromatic, undergoing successive stages of karyopycnosis, ending in extreme cases in karyorrhexis. Sometimes, however, it becomes hypochromatic, and undergoes karyolytic changes.

It is somewhat remarkable that these characteristic changes during inanition,—cell-atrophy with characteristic, more or less extensive nuclear and cytoplasmic degeneration,—are likewise found to a greater or less extent associated with a wide range of other conditions. In the foregoing pages, changes in thyroid structure somewhat similar to those associated with the various degrees of inanition have been mentioned in connection with the following:

1. Spontaneous (?) degeneration (in normal animals without apparent cause).
2. Age changes (tendency of cells to become flattened with age; senile atrophic changes).
3. Functional changes (varied changes due to functional activity; atrophy in the exhaustion following hyperactivity).
4. Changes due to effects of diet (meat and other special diets; administration of iodine).
5. Toxic effects (changes produced by injection of various toxic substances, proteid extracts, etc.).
6. Circulatory disturbances (stasis produced by ligation of vessels, etc.).

7. Pathological conditions (thyroiditis, exophthalmic goiter, etc.), probably due to infections.

8. Results of imperfect fixation.

9. Post mortem changes (due to mechanical injury, post mortem autolysis, etc.).

To this should be added the statement that very similar cell-changes have been described, especially by pathologists, in various tissues of the body, most frequently in the epithelia of the various parenchymatous glands. Changes in the renal epithelium following ligation of vessels, infarcts, intoxications, infections, post mortem changes, etc., form a familiar example, in which the phenomena are in many respects strikingly similar to the degenerative changes above described for the thyroid gland.

The remarkable similarity in the degenerative changes thus found in various organs and under apparently widely different conditions naturally raises the question as to whether the underlying fundamental process may not be at least in some respects essentially similar in all cases. It may be possible, for example, that cellular inanition may be produced in different ways, and may therefore be the essential factor in the process of degeneration arising from varied causes. If, as is now generally assumed, cellular metabolism is accomplished by means of numerous varieties of intracellular enzymes, one could easily understand how anything which would destroy or interfere with the activity of any of the enzymes necessary to anabolism might thereby produce a condition of cellular inanition, even in the presence of an abundant food-supply. The probable importance of autolytic enzymes in the phenomena of cell-degeneration, especially in the nuclear changes of pycnosis, karyolysis, etc., has been emphasized by Wells ('14) and others. A final solution of the problem is impossible at the present time, on account of our scanty knowledge of normal cell-physiology; but it seems probable that many of the phenomena of cellular degeneration from various apparent causes will ultimately be explainable as due essentially to cell-inanition.

THE PARATHYROID GLAND

The normal structure of the parathyroid glands will be considered first, followed by a discussion of the changes produced during inanition.

a. Normal structure of the parathyroid glands

As is well known, there is in the rat a single pair of parathyroid glands, said to correspond to parathyroid III. In one exceptional case, I found a parathyroid (see table 1) on one side only. I have never observed the accessory parathyroids described by Erdheim (cited by Biedl '13). The parathyroids are located upon the external surface of each lateral lobe of the thyroid gland, usually somewhat posteriorly, though occasionally more anteriorly (figs. 1, 3, 4, 5, 6).

Ochsner and Thompson ('10) state that the parathyroids of the rat are located within the thyroid lobes near the upper pole. I find, however, that there is considerable variation; they occur slightly more frequently opposite the middle third of the thyroid lobe, but often at more cephalic or caudal levels. Of 59 glands whose position was noted, 18 were located in the cephalic third of the thyroid, 20 in the middle third, 13 in the caudal third, 6 at the junction of the cephalic and middle thirds, and 2 at the junction of middle and caudal thirds. The parathyroids of the two sides are usually, but not always, at nearly the same level. In 3 cases observed, one parathyroid was located in the cephalic third of the lateral lobe of the thyroid, while the opposite parathyroid corresponded to the caudal third of the thyroid.

The parathyroid gland lies partly embedded within the thyroid, about one-fourth to one-third of its surface usually forming an external free or exposed surface (figs. 1, 3, 4, 5, 6). Sometimes it may project more extensively from the thyroid surface; in other cases it lies more deeply, rarely entirely embedded within the thyroid.

As to size, the dimensions of the parathyroid gland at various ages are given in the following table.

TABLE I

Dimensions of parathyroid glands in albino rats. Measurements from mounted sections

RAT NO. AND SEX	AGE	BODY-LENGTH mm.	BODY-WEIGHT GROSS (AND NET)	DIMENSIONS OF PARATHYROIDS		AVER. DIAM.
				a	b	
	days		grams	mm.	mm.	mm.
<i>A. Normal (control) rats</i>						
St 32.1 f	10	46	5.0(—)	0.22×0.18×0.26	0.26×0.18×0.26	0.23
V 2.1 m	14	89	22.7(—)	0.34×0.18×0.30	0.34×0.18×0.36	0.28
S 9.47 f	22	95	25.5(23.3)	0.33×0.32×0.38	0.28×0.38×0.38	0.35
St 32.2 m	21		27.2(—)	0.46×0.32×0.48	0.53×0.36×0.50	0.44
St 5.1 f	56		63.0(—)	0.62×0.56×0.62	0.56×0.50×0.52	0.56
St 12.54 f	110	166	121 (116)	0.96×0.58×0.72	0.83×0.64×0.72	0.76
S 5.4 f	74	168	126 (118)	0.64×0.50×0.40	0.54×0.50×0.36	0.49
St 10.24 f	117	169	135 (129)	1.21×0.65×0.90	0.94×0.70×0.90	0.88
H 24.3 f	232	188	143 (138)	0.66×0.56×0.88	0.50×0.56×0.72	0.64
H 65.7 f	98	179	144 (139)	0.57×0.43×0.64	0.55×0.40×0.80	0.57
H 60.3 f	78	182	146 (138)	0.47×0.58×0.74	0.75×0.48×0.74	0.63
H 68.3 f	74	185	158 (151)	0.45×0.48×0.58	0.46×0.48×0.52	0.50
H 42.3 f	182	195	170 (160)	0.55×0.64×0.74	0.78×0.60×0.70	0.67
S 5.3 m	74	180	172 (167)	0.62×0.36×0.47	(not observed)	0.48
H 47.3 m	145	201	174 (168)	0.54×0.64×0.72	0.66×0.54×0.80	0.65
H 27.3 f	253	195	175 (166)	0.84×0.58×0.90	0.89×0.60×0.80	0.77
MI 2 m	74	208	181 (173)	0.49×0.58×0.74	0.56×0.46×0.67	0.58
H 34.3 f	224	194	181 (173)	0.70×0.54×1.12	(1 gland absent)	0.79
H 34.6 f	225	205	194 (188)	0.57×0.70×0.86	0.84×0.56×0.76	0.71
S 33.116 f	340	195	194 (188)	0.79×0.60×0.86	0.90×0.68×0.70	0.76
H 70.3 m	70	194	208 (198)	0.63×0.48×0.80	0.79×0.53×0.80	0.67
H 27.6 m	254	214	229 (222)	0.75×0.75×0.85	0.88×0.60×0.80	0.77
H 50.3 m	141	211	230 (222)	0.75×0.60×0.90	0.77×0.72×0.90	0.77
S 14 x m	?	205	252 (247)	0.68×0.55×0.65	0.72×0.55×0.80	0.66
H 54.3 m	101	222	284 (275)	0.86×0.60×0.80	0.66×0.64×0.80	0.73
St 14 m	442	239	322 (314)	0.88×0.72×0.96	1.07×0.55×0.90	0.90

B. Rats at maintenance from 3 to 10 weeks of age

S 5.10 f	67	100	22.7(21.0)	0.49×0.40×0.42	0.52×0.37×0.50	0.45
S 11.63 f	72	95	23.8(22.6)	0.50×0.50×0.50	(not observed)	0.50
S 11.65 m	73	100	23.8(22.5)	0.48×0.44×0.53	0.47×0.48×0.52	0.49
S 11.64 f	73	100	24.2(22.9)	0.61×0.55×0.65	0.68×0.50×0.60	0.60
S 12.69 f	66	100	24.5(22.7)	0.43×0.50×0.65	0.46×0.55×0.55	0.52
S 6.23 f	72	102	26.1(24.5)	0.72×0.40×0.30	(not observed)	0.47
S 5.8 f	73	105	27.6(24.6)	0.50×0.45×0.35	0.50×0.45×0.35	0.43

TABLE 1—Continued

RAT NO. AND SEX	AGE	BODY-LENGTH <i>mm.</i>	BODY-WEIGHT GROSS (AND NET) <i>grams</i>	DIMENSIONS OF PARATHYROID'S		AVER. DIAM. <i>mm.</i>
				a	b	
	<i>days</i>			<i>mm.</i>	<i>mm.</i>	
<i>C. Adult rats with acute inanition¹</i>						
M 1 m	(?)	205	248 to 168(165)	0.50×0.60×0.80	0.45×0.64×0.80	0.63
M 2 m	(?)	(?)	254 to 170(167)	0.69×0.48×0.80	0.57×0.52×0.80	0.64
S 16 f	(?)	195	267 to 190(186)	0.75×0.51×0.52	0.78×0.50×0.55	0.60
S 27 m	(?)	215	320 to 223(219)	0.77×0.60×0.80	0.85×0.60×0.80	0.74
S 25 m	(?)	205	328 to 202(198)	0.73×0.52×0.70	0.88×0.58×0.66	0.68
<i>D. Adult rats with chronic inanition¹</i>						
M 3 m	(?)	175	188 to 125(122)	0.48×0.48×0.96	0.49×0.66×0.72	0.63
M 6 m	(?)	175	220 to 138(134)	0.35×0.45×0.70	0.35×0.70×0.75	0.55
M 11 m	(?)	190	264 to 163(158)	0.55×0.52×0.72	0.52×0.50×0.70	0.59

¹ Both initial and final body weights given.

In the first column, the letters 'St', 'V,' etc., refer to different series of rats used. The number preceding the decimal point is the litter number; the number following is the individual number. 'm' refers to male, 'f' to female. Under 'Dimensions of parathyroids,' the measurements for the two glands are listed separately in columns 'a' and 'b'.

The cephalo-caudal length (which is always the first of the three dimensions given in the table) was calculated from the number of sections, of known thickness, through which the gland extended. The other dimensions represent the largest and smallest diameters measured in the largest cross-section of the gland, in the mounted sections. It should be noted, therefore, that these dimensions are smaller than in the fresh gland, as each linear dimension has probably undergone a shrinkage of at least 10 per cent in the process of fixation, dehydration and embedding.

Generally speaking, the parathyroid presents a slightly flattened, ellipsoidal form; the relative dimensions usually corresponding in a general way to those of the associated lobe of the thyroid. That is, in cross-section the outline usually appears somewhat compressed medio-laterally; but the cephalo-caudal

dimension is greatest in less than half of the cases. It will be noted, however, that the parathyroid is frequently nearly spherical in form, the three axes being approximately equal (table 1; figs. 1 and 3 to 6).

The normal growth in the dimensions of the parathyroid is evident from the table. In the pair of newborn parathyroids, the average diameter is 0.23 mm.; at 2 weeks it is 0.28 mm.; at 3 weeks 0.35 to 0.44 mm.; and at 8 weeks, 0.56 mm. In 5 rats from 70 to 74 days of age, the average is 0.54 mm. (range 0.48 to 0.67 mm.). The dimensions increase very irregularly up to 0.90 mm. average in a rat of 322 g. gross body weight, 442 days of age.

In spite of the comparatively small number of observations and the admitted inadequacy of the average diameter as a measure of the size of the parathyroid, it is believed that these data are useful for purposes of general comparison. The data for the individual parathyroids were compared with the weights of the corresponding thyroids (not shown in the table), but there is apparently no close correlation between them.

A point of special interest, which is not apparent from casual inspection of the table, appears more clearly when the observations are plotted graphically according to the body weight and average diameter of the parathyroid. The gland appears to be relatively larger in the females. Further observations will of course be necessary to establish this point with certainty; but if true, this will place the parathyroid in a class with the hypophysis and suprarenals, in which the female rats possess relatively larger glands.

The normal structure of the parathyroid gland in the albino rat at 3 weeks of age is shown in figure 11. The epithelial cells are grouped in irregular, closely-packed masses, occasionally showing a cylindrical or cord-like arrangement.

In size the parathyroid epithelial cells vary considerably, the average being about 6 x 8 micra, or slightly larger. They are thus considerably smaller than the thyroid epithelium of a corresponding gland. The cell boundaries are usually distinct.

The cytoplasm is relatively small in amount, forming a narrow zone 1 to 2 micra in width adjacent to the nucleus. The cytoplasm is usually finely granular, pale reddish-violet in appearance (with Zenker fixation and haematoxylin-eosin stain). No 'oxyphile' (eosinophile) cells are present.

The nuclei of the parathyroid epithelium (fig. 11) vary considerably. They usually appear elongated, the smaller rounded forms perhaps representing cross-sections of ellipsoidal nuclei. There is considerable variation in size (average about 4 x 6 micra) and form. The nuclear outline frequently presents a notched or lobulated appearance.

In structure, the parathyroid nuclei are similar to those of the thyroid, presenting a distinct, deeply-staining nuclear membrane, and a faint nuclear network with usually one or two distinct nucleoli (karyosomes), in a clear, light, homogeneous background corresponding to the nuclear sap (karyolymph). Mitoses are relatively abundant at this stage, two or three being found in each cross-section near the center of the gland.

The parathyroid gland, like the thyroid, is in general fairly uniform throughout in structure at this time, but certain irregularities may appear, even at this age. In the most superficial stratum of the gland, especially on the external free surface (not in contact with thyroid) modified cells may appear. These cells usually form small groups of somewhat atrophic appearance. The cytoplasm is more irregular, vacuolated or denser and deeply-staining. The nuclei of these cells are generally somewhat smaller than usual, often flattened, and with more or less deeply-staining homogeneous appearance characteristic of the earlier stages of pycnosis. Such atrophic cells rarely occur except near the surface, and perhaps represent a mild form of pressure-atrophy (as found also near the surface in the thyroid).

The interstitial connective tissue forms a delicate, fibrous stroma, like that of the thyroid, except that it is usually not so highly vascular (fig. 11). In a few places, it is somewhat more abundant, forming scattered, irregular, light streaks observed in the interior of stained cross-sections. These streaks apparently become more distinct in the older rats.

In the parathyroid at 10 weeks, the structure is essentially the same as at 3 weeks (fig. 11), no important change in the appearance or average size of the cells being observed. Mitoses appear somewhat less frequently, only 1 or 2 in a section. The atrophic or degenerated types appear usually somewhat more frequently and more pronounced in character, however. They most commonly appear in the superficial stratum, especially at the exposed surface (not in contact with thyroid); but occasionally in the interior also, usually in scattered areas. The nuclei of these cells are usually deeply-staining and pycnotic, though vesicular karyolytic forms also occur. The cytoplasm in these atrophic types is usually rarefied and vacuolated in appearance, but occasionally somewhat coarsely granular and deeply-staining (eosinophile), suggesting in some respects the 'oxyphile' type described as normal by some authors for the

Fig. 11 A small portion of the parathyroid gland shown in figure 1 (rat S 9.47, normal 3 weeks), magnified to represent the details of the normal histological structure (which is essentially the same as at 10 weeks). Epithelial cells in irregular masses; cytoplasm granular, scanty in amount; nuclei irregularly elongated in appearance. Stroma scanty, vascular. ($\times 750$.)

Fig. 12 A small portion of the parathyroid gland shown in figure 4 (rat No. S 11.63, held at maintenance from 21 to 72 days of age), magnified to show details of histological structure. This area represents the hypochromatic (incipient karyolytic) type, which is relatively infrequent. The nuclei appear light and swollen. The cytoplasm here is apparently not reduced in amount, but shows tendency to vacuolization and disappearance of the normal granulation. Stroma normal. ($\times 750$.)

Fig. 13 A small portion of the parathyroid gland shown in figure 5 (rat No. S 5.10, held at maintenance from 21 to 67 days of age), magnified to show the details of histological structure. This area represents the typical hyperchromatic type (various stages of karyopycnosis). Cytoplasm more or less reduced in amount, with marked vacuolization ('hydropic degeneration'). Stroma normal. ($\times 750$.)

Fig. 14 A small portion of the parathyroid gland shown in figure 6 (rat No. S 11.64, held at maintenance from 21 to 73 days of age), magnified to show the details of histological structure. This area represents a somewhat advanced stage of degeneration, which frequently involves small, scattered masses, but is rarely extensive. The nuclei are partly of the hypochromatic (karyolytic), and partly of the hyperchromatic (karyopycnotic) type. Around the former, the cytoplasm is usually vacuolated ('hydropic degeneration'); while around the latter type cytoplasm appears reduced in amount, deeply-staining (eosinophile) and frequently coarsely granular in appearance. ($\times 750$.)

parathyroid of various animals (including man). Sometimes spaces are seen between the larger bundles of connective tissue and the adjacent parenchyma. These spaces somewhat resemble in appearance the paratrabecular and subcapsular lymph-sinuses in lymph-nodes.

In the older and adult animals, the parathyroid gland shows essentially the same structure as described at 10 weeks. The cells average perhaps slightly larger, the nuclei being typically elliptical and averaging between 4×6 and 5×7 micra. The cytoplasm forms a light granular zone 1 to 2 micra in width. Mitoses are not found in the adult rats. The atrophic or degenerative types of cells occur frequently, though usually in limited, scattered areas, especially near the exposed surface of the parathyroid.

b. Structure of the parathyroid glands in young rats held at maintenance

If in the rats held at maintenance (constant body-weight) from the age of 3 to 10 weeks the dimensions of the parathyroid glands be compared with those of the controls at 3 and 10 weeks (table 1), it appears that the parathyroid has not shrunk in size during the experiment. On the contrary it has even apparently increased so that the dimensions are nearly as large as those of the full-fed controls of the same age but several times larger in body-weight. As shown in table 1, the average diameter of the normal parathyroid at 3 weeks is about 0.40 mm., at 10 weeks, 0.54 mm.; in maintenance 3 to 10 weeks, 0.49 mm. Thus the parathyroid in young rats held at maintenance becomes relatively very large in comparison with the thyroid (which usually decreases somewhat), as is apparent upon comparison of the parathyroids in figures 1 and 3 with those in figures 4, 5 and 6.

The changes in the histological structure of the parathyroid gland during inanition are on the whole less marked than in the thyroid gland, although in most respects similar in character. In the parathyroids of rats held at maintenance from the age of

3 to 10 weeks, the epithelial cells show a variety of changes in structure, but it is doubtful whether there is in most cases any marked decrease in the average volume of the cells.

The cytoplasm, however, has undergone structural changes similar to those described for the thyroid cells (though somewhat less marked), its finely granular structure usually showing more or less marked vacuolization or 'hydropic degeneration' (figs. 12, 13, 14). In some cases, however, especially with advanced karyopycnosis, the cytoplasm may appear somewhat diminished in amount, and with deeply-staining (eosinophile), coarsely granular structure. The cell-boundaries sometimes remain distinct (fig. 12), but are frequently indistinct (figs. 13 and 14).

Two distinct types of nuclear change occur (similar to those found in the thyroid). In the first or hypochromatic type (fig. 12) the nuclei appear vesicular, swollen and very lightly stained. This type is relatively less frequent (as in the thyroid) and may appear in all the cells over considerable areas (as in fig. 12), or in scattered cells or small groups (as in fig. 14). This type of nucleus probably represents an early stage of karyolysis, though it is doubtful whether any nuclei actually reach dissolution in the specimens studied.

As in the thyroid, the more frequent type of nuclear change in the parathyroid in young rats held at maintenance is in the direction of hyperchromatosis, representing various stages of karyopycnosis (figs. 13 and 14). For the most part, however, the parathyroid nuclei do not go beyond the earlier stages, merely showing a homogeneous background more deeply colored so as to obscure the internal nuclear structure. In these nuclei, there is little if any decrease in size, and this type frequently occurs throughout practically the entire gland. Less frequently more advanced stages of pycnosis are found, in which the nuclei are diminished in size, with homogeneous deep stain (fig. 13). The hyperchromatic and hypochromatic types of cell-degeneration may sometimes occur intermingled, as in figure 14.

No advanced stages involving karyorrhexis were found. Neither mitosis nor amitosis was observed in any case.

The interstitial tissue or stroma of the parathyroid rarely shows any noteworthy changes. In some cases it appears slightly increased in amount, with edemic appearance, but not so often as in the thyroid.

c. Structure of parathyroid in adult rats after acute and chronic inanition

In adult rats subjected to acute or chronic inanition, the dimensions of the parathyroid gland are given in table 1. While it is impossible to draw any final conclusion, on account of individual variation and the small number of observations, there seems to be a decrease in the size of the parathyroid as a result of inanition. When the average diameters and corresponding (final) body-weights are plotted graphically, the parathyroids appear approximately normal. Their decrease during inanition therefore would appear to be nearly proportional to that of the whole body.

In histological structure, the parathyroids in adult rats after acute and chronic inanition show changes essentially like those described for the younger maintenance rats. The changes are in general less marked than in the thyroid, but there is considerable individual variation. Although there is cell-shrinkage in some places, especially where degeneration is marked, in other places there appears no decrease in the average size of the parathyroid cells.

The cytoplasm in adult parathyroids following inanition sometimes appears nearly normal, but usually shows typical vacuolization ('hydropic degeneration'), or in some cases a more deeply-staining homogeneous or coarsely granular structure (especially accompanying markedly pycnotic nuclei).

The nuclei may be nearly normal, but usually show hyperchromatic changes (more rarely hypochromatic), being usually found in the earlier (rarely later) stages of karyopycnosis. These changes occur not merely in restricted areas, or near the free surface (as found in the normal gland) but usually and typically involve large areas and frequently the entire gland. Thus while

no new types of cells occur, the atrophic types which occur infrequently and in small amount in the normal gland become very frequent and extensive during inanition. The changes in general appear to be somewhat more marked and extensive during chronic than during acute inanition, although there are individual variations.

The interstitial connective tissue or stroma of the parathyroid appears usually somewhat more distinct, and often relatively increased slightly in amount, during acute and chronic inanition of adults.

d. Discussion and conclusions

Broadly speaking, we may conclude from the foregoing that in general the effects of inanition upon the parathyroid gland are similar to those on the thyroid, but somewhat less marked. The similarities and differences include the following.

The parathyroid gland apparently belongs to that group of organs which in young rats tend to continue growth, even when the body-weight is held constant. This group includes the eye-balls, spinal cord, testes, skeleton, alimentary canal, suprarenal glands and hypophysis. The thyroid, on the contrary, belongs to the group losing weight (Jackson '15 b).

In the parathyroid, many of the individual cells apparently do not decrease in size during inanition; whereas in the thyroid the decrease is usually well marked, especially in the cytoplasm.

In both parathyroid and thyroid glands, the cytoplasm usually shows marked changes during inanition, whether or not it is decreased in amount. Vacuolization ('hydropic degeneration') is most frequent, but deeply-staining, eosinophile condensations of homogeneous (especially in the thyroid) or coarsely granular (especially in the parathyroid) types may occur.

The nucleus in both parathyroid and thyroid glands during inanition tends to become hyperchromatic (more rarely hypochromatic). Thus the nuclei are commonly found in various stages of pycnosis, the earlier stages being typical in the parathyroid, while in the thyroid the later stages (and even karyorrhexis) may frequently occur.

In both parathyroid and thyroid (especially the latter) the normal structure is somewhat variable, and a few cells of atrophic, degenerative character occur. These atrophic types become much more pronounced and numerous during inanition.

The fibrous interstitial tissue (stroma) undergoes little change during inanition, though sometimes it is increased in amount by edemic infiltration (especially in the thyroid).

Very little is found in the literature concerning the effect of inanition upon the parathyroid glands. Erdheim ('03) finds in the human parathyroid small droplets or granules of a fatty nature, which increase in number with age, and are apparently independent of the general nutritive condition of the body.

Pepere ('06) in his extensive work on the parathyroid gland mentions briefly (p. 265) some observations upon the effects of inanition on the parathyroid in dogs starved 9 to 27 days, and in two human cases of death from inanition following oesophageal obstruction. The parathyroid is found relatively less affected than any other viscera. In the dog there is atrophy of the parenchyma, especially of the cytoplasm, which becomes greatly reduced in amount, with vacuolization and loss of the characteristic granulation. The nucleus is hyperchromatic. In the human parathyroid, the effects of inanition are similar, including: "*rimpicciolimento dei corpi cellulari, diminuite le granulazioni protoplasmatiche, scarsissimi gli elementi cromofili, estese degenerazioni idropiche e vacuolari delle cellule, assente la colloide.*" Thus Pepere's observations upon the human and canine parathyroids are in general agreement with my findings in the rat, excepting that he does not mention the occurrence of (advanced) pycnosis or karyolysis.

According to Thompson ('06) the parathyroids in man cannot be said to have a distinct pathology, although various degenerations and other pathologic conditions have been described. He cites the work of Peterson and of Benjamins, in which parenchymatous atrophy, hydropic degeneration, etc., are shown to occur frequently in the human parathyroid.

Following the description by Welsh ('98) there are generally described in the parathyroid of man (and some of the lower ani-

mals) two types of cells: (1) 'principal' cells described by Welsh as having in man "a relatively small and clear protoplasmic body, and a relatively large and clear nucleus." These cells constitute the chief part of the gland, and are constantly present. (2) The 'oxyphile' cells usually have relatively more cytoplasm, finely granular and sometimes finely vacuolized. The nucleus is both relatively and absolutely smaller than in the 'principal' cells, its outline more circular and chromatin more dense, "so that no nuclear network can be detected and the entire nuclear mass appears uniformly and deeply stained." These 'oxyphile' cells are found by Welsh in a very large proportion of cases, though not all, and never so abundantly as the 'principal' cells. They never form a large proportion of the gland, and may occur as small masses (often just beneath the capsule) or as scattered cells throughout the gland.

The presence of these 'oxyphile' cells has been confirmed in man and a part (not all) of the lower animals. They are generally considered to represent cells in functional activity. Against this view, however, is the fact that they are quite variable in appearance, and frequently absent altogether (sometimes in man; constantly in some of the lower animals, and especially in the young).

Although I have made no special study of the parathyroid in any other form, the conditions found in the rat lead me to suggest the possibility that these 'oxyphile' cells may represent merely atrophic types, with no functional significance. It will be noted that (although the cytoplasm is relatively abundant) the nucleus of these 'oxyphile' cells as described by Welsh and others corresponds closely with the pyknotic condition characteristic of atrophic, degenerated cells, such as are described above in the normal parathyroid and thyroid glands, and are increased in number during inanition. While the evidence at hand is insufficient for a final conclusion, it seems to me that this interpretation is a possibility which should be kept in mind during further investigation of the matter.

SUMMARY

The more important results of the present investigation may be summarized as follows.

In young rats held at maintenance for several weeks (and hence in a condition of chronic inanition), the histological changes in the thyroid are varied. The follicular epithelium is atrophied, with reduction in height. The nuclei are rarely hypochromatic (various stage of karyolysis), but hyperchromatosis is more typical, the nuclei usually presenting some stage of pycnosis. In the earlier stages the nucleus may be nearly normal in size and structure, excepting a pale, homogeneous coloration of the nuclear background. In more advanced stages, the nucleus diminishes in size, with deepened coloration, forming a dense, deeply-staining, homogeneous mass (typical pycnosis). In extreme cases the nucleus becomes fragmented (karyorrhexis). Neither mitosis nor amitosis is found.

The cytoplasm is usually reduced in amount considerably more than the nucleus. The cytoplasm may show no marked change in structure (simple atrophy), but usually becomes rarefied, with a marked vacuolization ('hydropic degeneration') and loss of the normal granulation. This is especially marked in the few cells where the cytoplasm has lost but little in volume. In some cases the cytoplasm may become homogeneous ('colloid' type) and in advanced stages may disintegrate, forming irregular, deeply-staining (eosinophile) masses of varied appearance.

The intrafollicular colloid may show no abnormal changes. Advanced stages of degeneration in the follicular epithelium, however, are accompanied by dissolution and disintegration of the colloid. The colloid is often replaced by desquamated epithelial cells in various stages of degeneration, and the entire follicle may collapse into an irregular mass.

The interfollicular connective tissue (stroma) usually shows no very marked change in structure, but is often increased in volume by an infiltration of ground substance, giving a somewhat edemic appearance. On this account, the whole thyroid

gland may show but little loss in absolute weight, although there has been a marked atrophy of the parenchyma.

In the adult rats subjected to acute and chronic inanition, the changes in the structure of the thyroid gland are likewise varied, but in general similar to those found in the younger rats. The interpretation of the changes in the older rats is more difficult, on account of the frequent occurrence in the normal (control) rats of degenerative changes somewhat similar to those found in advanced stages of inanition.

These changes, involving desquamation and degeneration of the follicular epithelium, have frequently been observed in the thyroids of rats both normal and under various abnormal conditions. They also occur as pathological changes in various other glands. It is suggested that the similarity of these cell-changes may possibly be due to cell-inanition as a common underlying factor.

The parathyroid glands appear to be relatively larger in the female. They apparently belong to that group of organs in which growth persists in young rats, even when held at maintenance (constant body weight) by underfeeding. In adult rats during acute and chronic inanition, the reduction in the size of the parathyroids is nearly proportional to that of the body as a whole.

In histological structure, the parathyroid gland is relatively more resistant than the thyroid to inanition. The changes in the structure of the epithelial cells are somewhat similar to those described for the thyroid, though in general less marked. In many of the cells there is apparently no decrease in the average size, but some (especially those degenerated) show marked shrinkage. The nuclei may remain nearly normal in size and structure, though usually exhibiting various stages of (rarely) karyolysis or (more frequently) karyopycnosis. No cell-division is found. The cytoplasm may be either somewhat reduced in amount, sometimes deeply-staining ('oxyphile'), or may remain nearly normal in volume, with marked vacuolization ('hydropic degeneration'). The stroma may remain normal in

amount, but is occasionally increased in volume by infiltration of ground substance.

Variations also occur normally in the structure of the parathyroid (though less marked than in the thyroid), so that here likewise caution must be observed in drawing conclusions as to effects of experiments. The 'oxyphile' type of cell does not appear to be a normal constituent of the parathyroid gland in the rat. However, some of the degenerated cells resemble in many respects the usual description of this 'oxyphile' type, which therefore may possibly represent an atrophic rather than a functional condition.

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