Band 39 · Heft 3

Ergebnisse der Anatomie
und Entwicklungsgeschichte
Reviews of Anatomy
Embryology and Cell Biology
Revues d'anatomie et de
morphologie expérimentale

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Springer-Verlag
Berlin Heidelberg GmbH

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With 33 Figures

Springer-Verlag Berlin Heidelberg GmbH 1967

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ISBN 978-3-662-23513-3 ISBN 978-3-662-25584-1 (eBook)
DOI 10.1007/978-3-662-25584-1

Ursprünglich erschienen bei Springer-Verlag Berlin Heidelberg New York 1967.

Library of Congress Catalog Card Number 64-20582
Titel-Nr. 4455.

Contents

Introduction

The histological structure of the thyroid gland is relatively simple, but the interpretation of the histological picture of individual glands examined is not always easy. The structural relation is so variable that it is often difficult to determine whether the gland is within normal range or not, so that interpretation tends to become more or less subjective and empiric. As stated by WEGELIN (1926), the variation may depend upon the characteristic state of the thyroid gland as a ductless gland, closely resembling an alveolar gland with a collecting duct system and accumulating colloid in the follicles. The colloid contained may be abundant or scarce, depending upon the requirement of the animal body and the intensity of secretory stimulation, resulting in the pattern of the parenchyma, especially the follicles, to be also variable. This state is particularly exaggerated in the human thyroid gland (HINTON, 1931; BIANCHEDI, 1934; ROSENKRANZ, 1935), and influenced by different complicated conditions of individual life, it becomes very difficult to analyze the histological pictures presented. Notwithstanding current interest in the physiology of the human thyroid gland in relation to pathology and disease, little work has been done to elucidate its histology, especially its developmental histology. Only some authors (HESSELBERG, 1910; ISENSCHMID, 1910; SANDERSON-DAMBERG, 1911; BÜCHNER, 1924; COOPER, 1925; MAY, 1928; SCHAER, 1928; DE OCA, 1930; ORATOR and SCHLEUSSING, 1931; RICE, 1931; HELLWIG, 1933; SAKA, 1935) have repeated histological studies on the human thyroid gland at different periods of postnatal life, but the human specific train of histological events noted from the newborn stage to senility has not been described in detail. No precise quantitative data, or if any, only a little are presented here and there. The present work constitutes the second part of studies on the histological development of the human thyroid gland (prenatal development — TAKI, 1958; SUGIYAMA et al., 1959a and b), based upon quantitative measurements of the gland with non-pathological materials. It helps to elucidate the serial steps in postnatal differentiation of the human thyroid gland, as well as assists assessing the histological variations during different periods of life.

Material and Methods

Thyroid glands of 326 cadavers ranging in age from immediately after birth to 88 years of age were collected for this study from the district around Nagoya City which is situated in the Plain of Nohbi, one of the littoral plains in Japan. One half of the glands were removed bilaterally or unilaterally from cadavers after postmortem examination in the Departments of Pathology and Forensic Medicine, Nagoya University School of Medicine, and the other half in toto from students' dissection material in the Department of Anatomy. Causes of death of the cadavers were mostly violence, accident and suicide or different diseases, as summarized in Table 1. Clinical and pathological records of each cadaver were reviewed as carefully as possible, especially in regard to history which could be related to thyroid diseases. All cadavers which indicated any evidence of abnormality of the thyroid gland were excluded from this study. Thyroid glands were fixed in 10% formalin solution or sometimes in Helly's and Ciaccio's fluids. Right (or left) lobes and those with the isthmus were transversely sliced into 5 pieces by safety razor blades. Further, 20 pyramidal lobes were sliced into two longi-

Table 1. *Materials examined*

Diagnosis given before or after death	No. of cases examined				
	Newborn to puberty 0—15 yrs	Early adult life 16—24 yrs	Late adult life 25—44 yrs	Presenium 45—49 yrs	Senium 50—88 yrs
Infection					
Pneumococcal pneumonia	2* (0)**	—	1 (0)	2 (0)	4 (1)
Pulmonary tuberculosis	1 (0)	1 (0)	8 (2)	2 (0)	14 (3)
Poliomyelitis	1 (1)	—	—	—	—
White straining	3 (0)	—	—	—	—
Intoxication					
Hypnotic poisoning	—	—	11 (2)	1 (1)	1 (0)
Others	4 (2)	3 (2)	1 (1)	—	—
Digestive system					
Cancer of tongue	—	—	—	—	1 (0)
Varix of esophagus	—	—	—	—	1 (0)
Stomach ulcer	—	—	—	—	1 (0)
Stomach cancer	—	—	2 (0)	1 (0)	6 (2)
Acute hepatitis	—	—	1 (0)	—	—
Hepatic coma	—	—	1 (0)	—	1 (0)
Liver cirrhosis	—	—	—	1 (0)	—
Pancreas tumor	—	—	2 (0)	—	—
Acute colitis	—	—	—	—	2 (0)
Ileus	—	—	—	—	1 (0)
Respiratory system					
Cancer of larynx	—	—	—	—	1 (0)
Aspiration pneumonia	—	—	—	—	1 (0)
Acute bronchopneumonia	—	—	—	—	1 (1)
Acute bronchitis	1 (1)	—	—	—	—
Kidney					
Acute nephritis	—	—	—	1 (0)	2 (0)
Chronic nephritis	—	—	—	—	1 (0)
Cystic kidney	—	—	1 (0)	—	—
Blood					
Acute myeloid leukemia	3 (2)	2 (2)	1 (1)	—	—
Purpura	—	1 (0)	—	—	—
Cardiovascular system					
Cardioplegia	—	1 (0)	2 (0)	1 (0)	4 (1)
Acute cardiac insufficiency	1 (0)	1 (1)	1 (1)	3 (1)	8 (1)
Cardiac weakness	—	—	4 (0)	—	6 (3)
Cardiac aasmus	—	—	—	—	3 (1)
Auricular septal defect	1 (1)	—	—	—	—
Fallot's disease	1 (0)	—	—	—	—
Congestive heart	—	—	1 (0)	—	2 (0)
Coronary insufficiency	—	—	—	—	1 (0)
Hypertension	—	—	—	—	1 (1)
Cor pulmonare	—	—	—	—	3 (1)
Acute endocarditis	1 (1)	—	1 (1)	—	—
Arteriosclerosis	—	—	—	1 (0)	2 (2)
Nervous system					
Schizophrenia	—	—	1 (0)	—	3 (1)
Cerebral bleeding	—	—	1 (0)	2 (0)	14 (5)
Cerebral arteriosclerosis	—	—	—	—	2 (2)
Cerebromalacia	—	—	—	—	4 (0)
Cerebral tumor	2 (2)	—	1 (0)	—	—

Table 1 (continued)

Diagnosis given before or after death	No. of cases examined				
	Newborn to puberty 0—15 yrs	Early adult life 16—24 yrs	Late adult life 25—44 yrs	Presenium 45—49 yrs	Senium 50—88 yrs
Others					
Senility	—	—	—	—	9 (5)
Ewing's sarcom	—	1 (0)	—	—	—
Mamma cancer	—	—	1 (1)	—	1 (1)
Violence and accident	11 (5)	12 (2)	18 (1)	4 (1)	7 (0)
Scleroderma	—	1 (1)	—	—	—
Hanging	—	—	4 (0)	—	1 (0)
Not recorded	17 (9)	13 (4)	16 (2)	5 (1)	28 (5)
Total no. 326 (88)	49 (24)	36 (12)	80 (12)	24 (4)	137 (36)

* Total no. of cases.

** Figure in parentheses: No. of women's cases.

tudinal pieces. The pieces were observed without any treatment at low magnifications by the binocular stereo dissection microscope to study the coarse histological appearance and at the same time to find other abnormal conditions. Materials examined histologically in detail consisted of a series of one or two pieces of the middle part of the lobe, most of which had the isthmus, and further the pieces of the pyramidal lobe. These pieces were embedded in celloidin or in paraffin, sectioned serially at 8 to 20 μ in thickness and stained with Hansen's hematoxylin and eosin. Some of the thin sections from the pieces fixed in Helly's fluid were stained by Bielschowsky's silver impregnation method and were used for making wax plate reconstruction models of follicles and folliculograms (Sugiyama and Ohida, 1954), in order to clarify the follicular relations accurately. Furthermore, the following measurements were made in relation to the follicles, follicle cells and capsule and interstitium in a well-prepared section 20 μ in thickness. The estimation of these values was useful for expressing accurately the histological change of the human thyroid gland. Of 326 thyroid glands, 10 in toto together with the larynx, trachea and esophagus were serially sectioned and stained in the same manner.

1. Dimensions (long and short diameters) of 25 large follicles and 25 small follicles were measured respectively in 4 zones — the peripheral and central zones of the lobe, the isthmus and the pyramidal lobe. The averaged long and short diameters of the large follicles, their maximum and minimum values are indicated in Figs. 2 to 5 and Table 9.

2. Measurements of follicles contained per mm^2 area were made on the same section of the lobe. The one mm^2 areas examined were conveniently classified into two kinds, large follicle area and small follicle area. The large follicle area contained completely and incompletely less than 40 follicles and the small follicle area 40 or more follicles. The number of visual fields of one mm^2 examined varied depending upon the size of the section of the lobe, the number for small follicle areas being usually over 50, and that for large follicle areas below 50. The numbers of follicles contained in the large follicle area and in the small follicle area were respectively averaged in each case, and the averaged, maximum and minimum values are indicated in Fig. 1. For the measurements, a central part of the ocular net micrometer was designed to indicate accurately a regular square of one mm^2 on the objective field at the magnification of 20. The section to be examined was consecutively moved down, to the right, up and to the right, in a manner similar to that for differential count of white cells.

3. Dimensions of commonly predominant, ordinary small follicles and ordinary medium-sized follicles were also observed by measuring their long and short diameters. 4. One to several large follicles closely packed in groups were observed in different zones of the same section of the lobe by estimating their extent and number. 5. Furthermore, the heights and widths of the follicle cells, and the long and short diameters of their nuclei were measured. 6. The widths of the capsule and septums were measured in the same section.

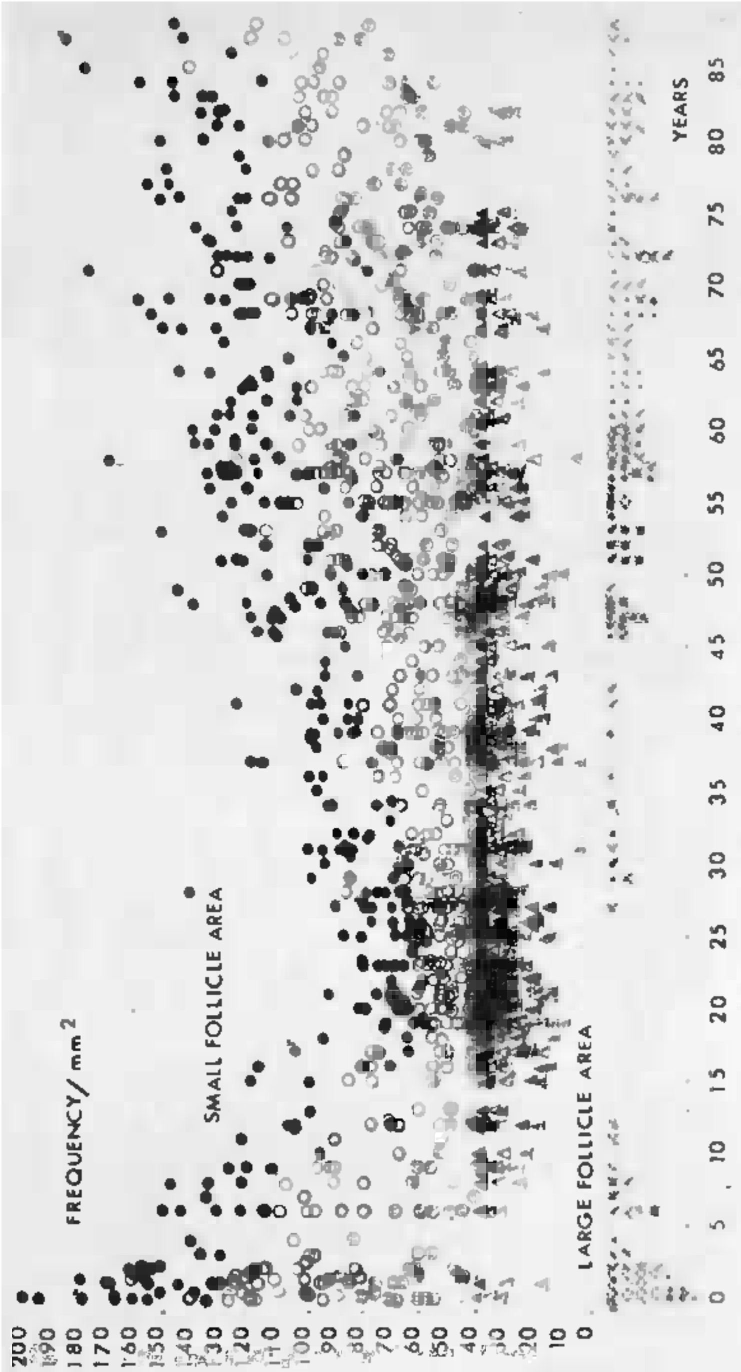

Fig. 1. Scatter diagram indicating age change of the thyroid parenchyma — estimated by measuring the frequencies per square millimeter of occurrence of follicles. The frequency values found on and over the border line which passes through 40, represent those of the small follicle areas, and the frequency values below 40 those of the large follicle areas. Each signal represents the value based upon measurements of each case. Note: ● : the maximum value of frequency per square millimeter of follicles in the small follicle area. ○ : the averaged value and ◎: the minimum value. ▲: the maximum value of frequency per square millimeter of follicles in the large follicle area. △: the averaged value and ◬: the minimum value. ✱ : the case where large follicle areas are not found in a gland. Signals of the same and near values in the same age are often overlapped

Folliculograms made it easily possible to clarify quantitatively the follicular relations such as the association and dissociation and outpocketings of the follicles and further provided a means of estimating the craniocaudal diameters of the follicles (Tables 2 to 4).

The life span of the cadavers used in the present study was conveniently divided into the following periods: The newborn period: Immediately after birth to not over one month; The suckling period: one month to not over one year; early childhood: one year to 5 years old (but not over 6 years); late childhood: 6 to 12 years; puberty: 13 to 15 years; early adult life: 16 to 24 years; late adult life: 25 to 44 years; presenium: 45 to 49 years and senium: 50 years to the eighties.

Observations

1. Follicles

a) General

The human thyroid gland appeared already well-developed immediately after birth and showed histologically no fundamental difference from the adult gland (Figs. 6 to 16). Shortly after birth, the follicles remained still associated with each other directly without communication of their cavities, and retained an embryonic pattern (HEIDENHAIN, 1921; LOESCHCKE, 1937; KULENKAMPFF, 1950; TAKI, 1958; SUGIYAMA et al. 1959b) (Fig. 30). This was also confirmed by analyzing the folliculograms prepared in the present study (Table 2). In a case of premature birth (corresponding to 32 weeks of prenatal life), this was exaggerated and indicated that all of the small and medium-sized follicles have always one to a few connections and some of the large follicles of over 200 μ have about 11 connections with other neighboring follicles (Table 3). Two months after birth (SUGIYAMA et al., 1958), the association decreased in number and the associated follicles were 50 to 78% of the follicles examined. Nine months to one year and a half, most of the follicles became dissociated except for small follicles. They were more often dissociated in the peripheral zone of the lobe. In two years, the follicles were almost completely dissociated in both the peripheral and central zones of the lobe and thereafter the follicle association disappeared.

The follicles varied in diameter from 20 μ to rarely over 1000 μ in young and late adults. These exceptionally large follicles of over 1000 μ persisted to occur as cysts further in the presenium and senium. Very small follicles were usually 20 to 35 μ in the long diameter while ordinary small follicles were about 70 to 90 μ and ordinary medium-sized follicles 100 to 200 μ. Ordinary large follicles were about 500 to 800 μ in the long diameter and in average 400 to 600 μ (Figs. 2 to 5). Between these ranges, there were frequently found follicles of other different diameters. The large follicles indicated generally greater values in the peripheral zone of the lobe, especially in its posterior part, than in the central zone. In the isthmus, they showed generally lower values than in the central zone of the lobe (Figs. 2 to 5). Examination of several cases of the pyramidal lobe showed that the large follicles have least values here (Table 9). Bands and islets consisting of numerous very small follicles and small follicles sometimes remained in adult life, further in the presenium and senium, not only in the peripheral zone of the lobe — just beneath the capsule, especially beneath its medial part —, but also in the central zone — just near the septums — generally in connective-tissue-abundant regions (Figs. 12 to 16).

The craniocaudal diameters of the follicles were investigated by making the folliculograms. The relation between the craniocaudal diameter and the long and short diameters obtained in transverse sections of the lobe was elucidated. For this purpose, the follicles were expressed as triangles consisting of three diameter lengths. By examining in this way, it was elucidated that most of the follicles are triangles, but a few — tubular follicles did not produce triangles. These tubular

Table 2. *Association and dissociation of follicles in follicle groups selected at random in the intermediate, peripheral and central zones of the lobe of the human thyroid glands at different life periods*

Craniocaudal diameters of follicles	Total number of follicles	Associated follicles	dissociated follicles	Total number of follicles	Associated follicles	dissociated follicles
10 hours after birth*	Intermediate zone					
D** ≦ 30 μ	43	43 (100%)	—			
30 < D ≦ 50	54	54 (100%)	—			
50 < D ≦ 100	39	39 (100%)	—			
100 < D ≦ 200	14	13 (93%)	1 (7%)			
200 < D	2	2 (100%)	—			
9 months after birth	Peripheral zone				Central zone	
D ≦ 30 μ	20	19 (95%)	1 (5%)	19	16 (84%)	3 (16%)
30 < D ≦ 50	33	3 (9%)	30 (91%)	31	11 (36%)	20 (64%)
50 < D ≦ 100	56	2 (4%)	54 (96%)	49	9 (19%)	40 (81%)
100 < D ≦ 200	14	1 (7%)	13 (93%)	5	1 (20%)	4 (80%)
200 < D	1	—	1 (100%)	—	—	—
One year and a half	Peripheral zone				Central zone	
D ≦ 30 μ	—	—	—	—	—	—
30 < D ≦ 50	17	1 (6%)	16 (94%)	25	7 (28%)	18 (72%)
50 < D ≦ 100	54	3 (6%)	51 (94%)	48	10 (21%)	38 (79%)
100 < D ≦ 200	31	2 (6%)	29 (94%)	28	2 (7%)	26 (93%)
200 < D	4	—	4 (100%)	2	2 (100%)	—
Two years	Peripheral zone				Central zone	
D ≦ 30 μ	—	—	—	—	—	—
30 < D ≦ 50	1	—	1	—	—	—
50 < D ≦ 100	6	1 (16%)	5 (84%)	4	—	4 (100%)
100 < D ≦ 200	25	1 (4%)	24 (94%)	17	—	17 (100%)
200 < D	5	—	5 (100%)	2	—	2 (100%)
Three years	Peripheral zone				Central zone	
D ≦ 30 μ	—	—	—	—	—	—
30 < D ≦ 50	4	—	4 (100%)	6	—	6 (100%)
50 < D ≦ 100	27	—	27 (100%)	36	—	36 (100%)
100 < D ≦ 200	47	—	47 (100%)	40	—	40 (100%)
200 < D	7	—	7 (100%)	—	—	—
6 years	Peripheral zone				Central zone	
D ≦ 30 μ	1	—	1	—	—	—
30 < D ≦ 50	7	—	7 (100%)	2	—	2 (100%)
50 < D ≦ 100	36	—	36 (100%)	21	—	21 (100%)
100 < D ≦ 200	40	—	40 (100%)	60	—	60 (100%)
200 < D	15	—	15 (100%)	17	—	17 (100%)
17 years	Peripheral zone				Central zone	
D ≦ 30 μ	—	—	—	—	—	—
30 < D ≦ 50	3	—	3 (100%)	5	—	5 (100%)
50 < D ≦ 100	17	—	17 (100%)	30	—	30 (100%)
100 < D ≦ 200	13	—	13 (100%)	24	—	24 (100%)
200 < D	6	—	6 (100%)	3	—	3 (100%)

* Premature birth (corresponding to 32 weeks of prenatal life).

** Craniocaudal diameter.

Table 3. *Averaged numbers of connections per associated follicle in follicle groups selected at random in the intermediate, peripheral and central zones of the lobe of the human thyroid gland*

Craniocaudal diameters of associated follicles	No. of associated follicles	Polar connections	Central connections	Total no.	No. of associated follicles	Polar connections	Central connections	Total no.
10 hours after birth*	Intermediate zone							
$D \leqq 30\mu$	43	0.5 (0—2)**	0.7 (0—2)**	1.2				
$30 < D \leqq 50$	54	0.5 (0—2)	0.9 (0—2)	1.4				
$50 < D \leqq 100$	39	0.9 (0—5)	1.2 (0—4)	2.1				
$100 < D \leqq 200$	13	1.6 (0—3)	1.6 (0—6)	3.2				
$200 < D$	2	4.0 (3—5)	7.5 (7—8)	11.5				
9 months after birth	Peripheral zone				Central zone			
$D \leqq 30\mu$	19	—	1.1 (1—2)	1.1	16	0.3 (0—2)	0.8 (0—2)	1.1
$30 < D \leqq 50$	3	0.3 (0—1)	0.7 (0—2)	1.0	11	0.4 (0—1)	0.6 (0—2)	1.0
$50 < D \leqq 100$	2	—	1.5 (0—2)	1.5	9	0.7 (0—2)	0.6 (0—1)	1.3
$100 < D \leqq 200$	1	1.0	—	1.0	1	1.0	—	1.0
$200 < D$	—	—	—	—	—	—	—	—
One year and a half	Peripheral zone				Central zone			
$D \leqq 30\mu$	—	—	—	—	—	—	—	—
$30 < D \leqq 50$	1	—	1	1.0	7	0.1 (0—1)	0.9 (0—6)	1.0
$50 < D \leqq 100$	3	0.3 (0—1)	1.3 (1—2)	1.6	10	0.3 (0—1)	0.8 (0—2)	1.1
$100 < D \leqq 200$	2	0.5 (0—1)	0.5 (0—1)	1.0	2	—	1.5 (1—2)	1.5
$200 < D$	—	—	—	—	2	0.5 (0—1)	2.0 (1—3)	2.5

* Premature birth (corresponding to 32 weeks of prenatal life).

** Range.

Polar connections are found in the cranial and caudal polar areas of the follicles and central connections in the middle zone.

follicles were increased slightly in frequency in follicles of over 200 μ in diameter with age and occurred not only in the peripheral zone of the lobe but also in the central zone (Table 8).

Large follicles appeared singly but tended rather to be packed closely in groups of two to several, sometimes over 10, and produced an islet (Figs. 6 to 20). The single large follicles and the islets found in the lobe were scattered in a regular fashion — more frequently in the posterolateral and/or posteromedial parts of the peripheral zone and in the posterior half of the central zone, and sometimes abundantly in the following three angular zones, 1. between the posterolateral and posteromedial parts of the peripheral zone, 2. between the posterolateral and anterolateral parts, and 3. between the anterolateral and anteromedial parts. The large follicles found in the isthmus and pyramidal lobe appeared to be scattered without showing any regular fashion.

The single large follicle or the islet, as a core, was surrounded with a more or less broad layer consisting of smaller follicles which contained medium-sized and small follicles. The core and layer as a set may be called the thyromere (thyroid segment) (Figs. 6 to 20). Some of the thyromeres found just beneath the capsule and near the septums were devoid of surrounding smaller follicles in the side concerned. The thyromeres became smaller in size in the anterior part of the peripheral and central zones of the lobe and further in the isthmus and pyramidal lobe. In some cases, they were inversely exaggerated in size in these parts.

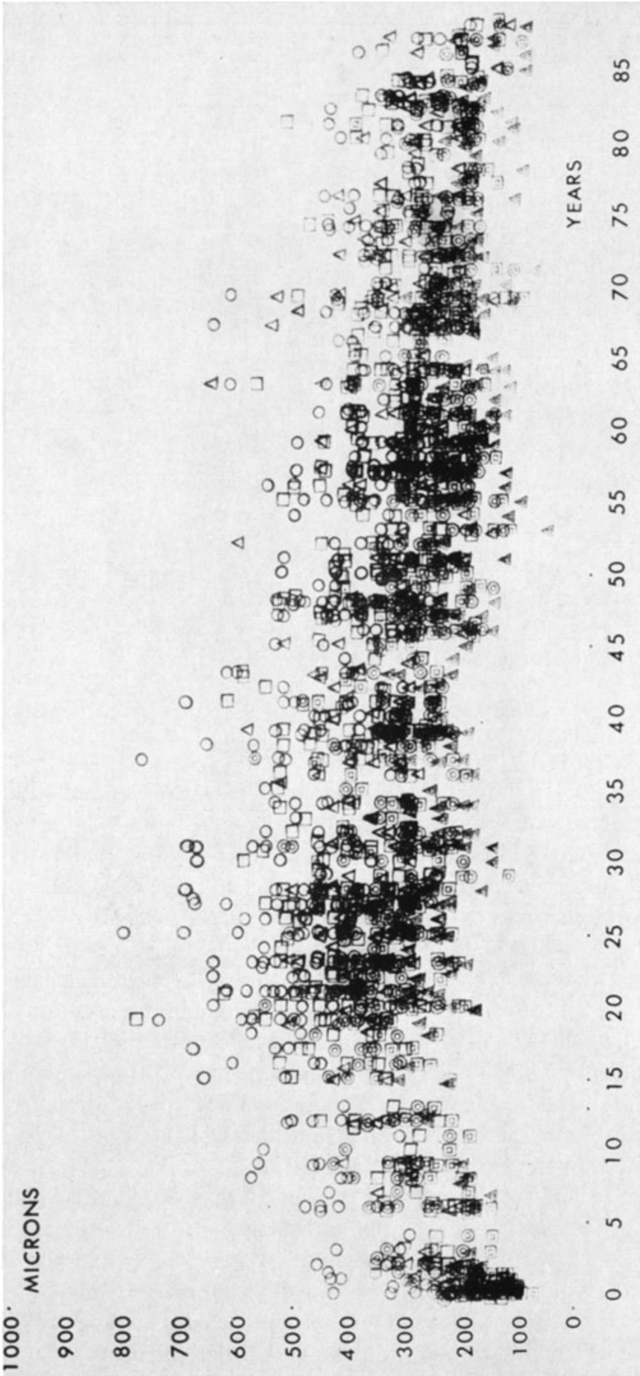

Fig. 2. Scatter diagram indicating age change of large follicles found in the peripheral and central zones of the lobe and in the isthmus, estimated by measuring the averaged long and short diameters. Each signal represents the averaged value of the diameters based upon measurements of each case. Note: ○ and ◎: averaged long and short diameters of large follicles found in the peripheral zone of the lobe. □ and ⊡: those found in the central zone of the lobe. △ and ▲: those found in the isthmus

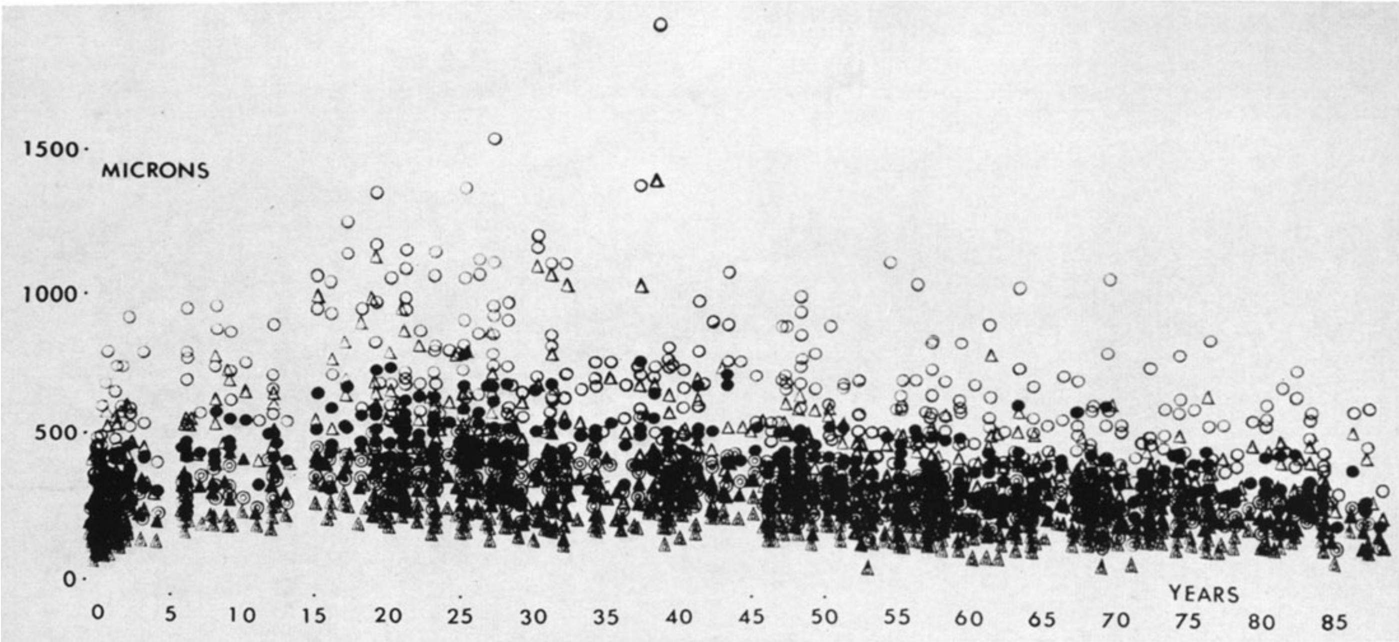

Fig. 3. Scatter diagram indicating age change of large follicles in the peripheral zone of the lobe, estimated by measuring long and short diameters (respectively, maximum, averaged and minimum values). Note: ○, ● and ◎: maximum, averaged and minimum values of the long diameter of the large follicles. △, ▲ and ◬: maximum, averaged and minimum values of the short diameter

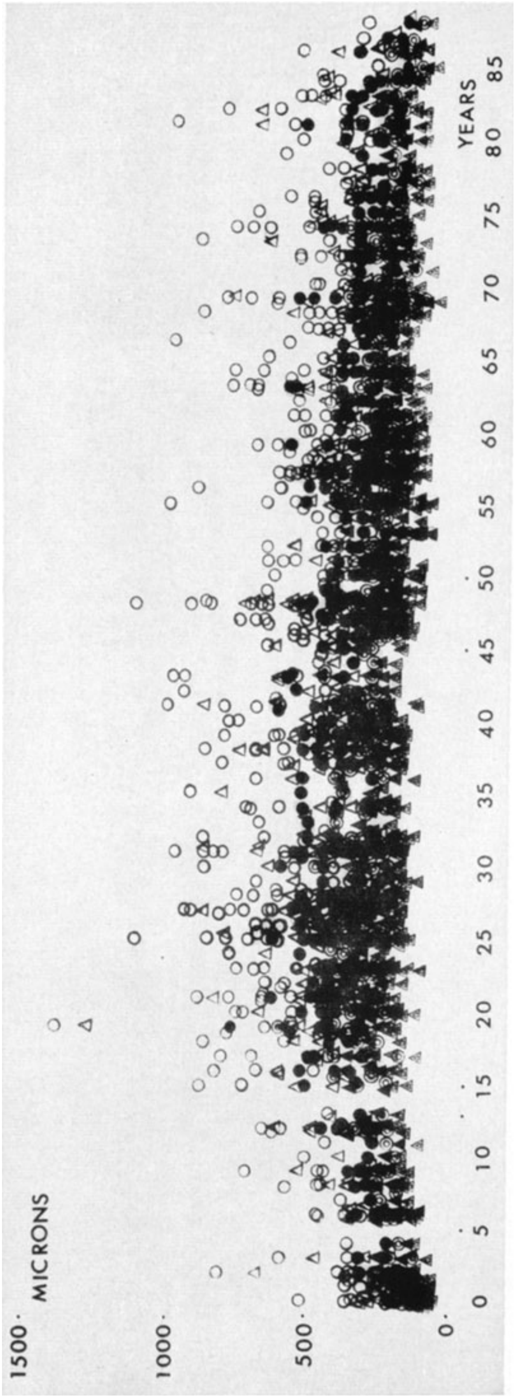

Fig. 4. Scatter diagram indicating age change of large follicles found in the central zone of the lobe, estimated by measuring long and short diameters (respectively, maximum, averaged and minimum values). Note: ○, ● and ◎: maximum, averaged and minimum values of the long diameter of the large follicles. △, ▲ and ◬: maximum, averaged and minimum values of the short diameter

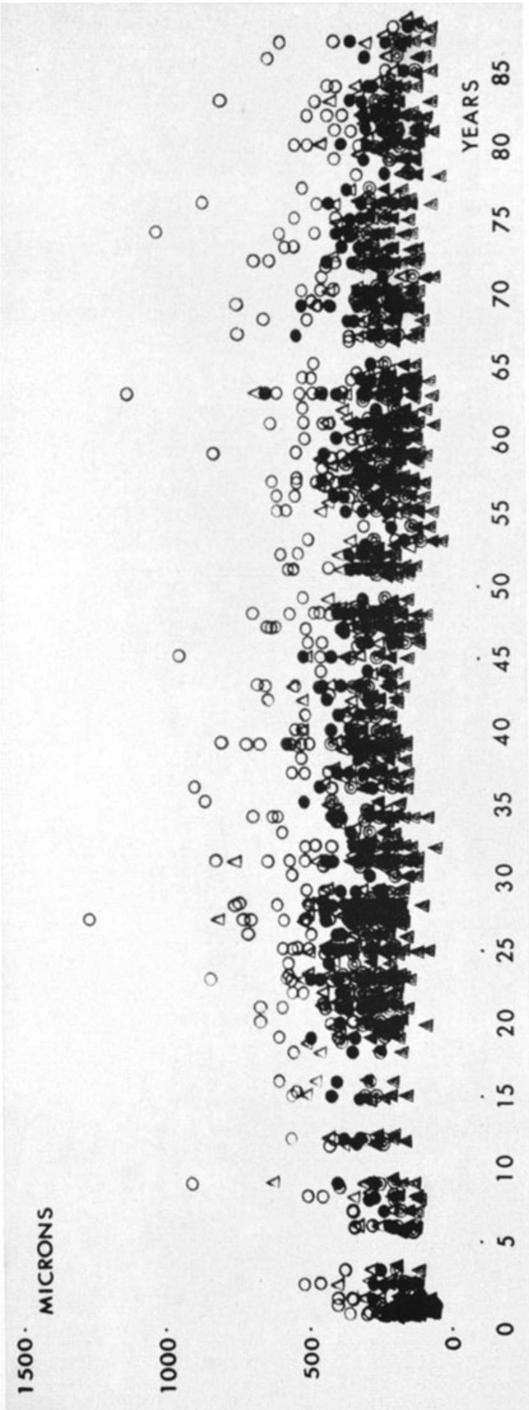

Fig. 5. Scatter diagram indicating age change of large follicles found in the isthmus, estimated by measuring long and short diameters (respectively, maximum, averaged and minimum values). Note: ○, ● and ◎: maximum, averaged and minimum values of the long diameter of the large follicles. △, ▲ and ◬: maximum. averaged and minimum values of the short diameter

Table 4. *Frequencies of acinar follicles and their alveolar pockets contained in follicle groups selected at random in the intermediate, peripheral and central zones of the lobe of the human thyroid gland*

Craniocaudal diameters of follicles	Total no. of follicles examined	No. of regular follicles	No. of acinar follicles	1 pockets	2	3	4	5	Total no. of follicles examined	No. of regular follicles	No. of acinar follicles	1 pockets	2	3	4	5
10 hours after birth*	Intermediate zone															
$D^{**} \leqq 30\ \mu$	43	43	0													
$30 < D \leqq 50$	54	54	0													
$50 < D \leqq 100$	39	39	0													
$100 < D \leqq 200$	14	14	0													
$200 < D$	2	2	0													
9 months after birth	Peripheral zone								Central zone							
$D \leqq 30\ \mu$	20	20	0						19	19	0					
$30 < D \leqq 50$	33	33	0						31	31	0					
$50 < D \leqq 100$	56	55	1 (2%)	1					49	49	0					
$100 < D \leqq 200$	14	12	2 (14%)	2					5	3	2 (40%)	2				
$200 < D$	1	1	0						0	0	0					
One year and a half	Peripheral zone								Central zone							
$D \leqq 30\ \mu$	0	0	0						0	0	0					
$30 < D \leqq 50$	17	17	0						25	25	0					
$50 < D \leqq 100$	54	53	1 (2%)	1					48	48	0					
$100 < D \leqq 200$	31	26	5 (16%)	3	2				28	20	8 (28%)	6	2			
$200 < D$	4	3	1 (25%)	1					2	0	2 (100%)		2			
Two years	Peripheral zone								Central zone							
$D \leqq 30\ \mu$	0	0	0						0	0	0					
$30 < D \leqq 50$	1	1	0						0	0	0					
$50 < D \leqq 100$	6	6	0						4	4	0					
$100 < D \leqq 200$	25	16	9 (40%)	5	4				17	9	8 (47%)	4	3	1		
$200 < D$	5	1	4 (80%)	2		1	1		2	1	1 (50%)		1			
Three years	Peripheral zone								Central zone							
$D \leqq 30\ \mu$	0	0	0						0	0	0					
$30 < D \leqq 50$	4	4	0						6	6	0					
$50 < D \leqq 100$	27	27	0						36	35	1 (3%)	1				
$100 < D \leqq 200$	47	44	3 (2%)	2	1				40	38	2 (5%)	2				
$200 < D$	7	6	1 (14%)		1				0	0	0					

6 years	Peripheral zone								Central zone						
D ≦ 30 μ	1	1	0						0	0	0				
30 < D ≦ 50	7	7	0						2	2	0				
50 < D ≦ 100	36	36	0						21	21	0				
100 < D ≦ 200	40	40	0						60	60	0				
200 < D	15	15	0						17	17	0				
17 years	Peripheral zone								Central zone						
D ≦ 30 μ	0	0	0						0	0	0				
30 < D ≦ 50	3	3	0						5	5	0				
50 < D ≦ 100	17	16	1 (35%)	1					30	29	1 (3%)	1			
100 < D ≦ 200	13	9	4 (30%)	1	1	2			24	20	4 (17%)	1	1	1	1
200 < D	6	1	5 (83%)	1		1	2	1	3	2	1 (33%)				1

* Premature birth (Corresponding to 32 weeks of prenatal life).
** Craniocaudal diameter.

The thyromeres were of smaller size in the newborn and suckling periods and again became so in the senium. The parenchyma found between the thyromeres was filled with medium-sized and small follicles. More closer observations showed that subordinate arrangements of the thyromeres can be found here. They consisted of a single or a few focal medium-sized follicles and surrounding small follicles.

Follicles, especially small follicles, were generally round to oval. Some of the follicles of over 100 μ in diameter became more or less irregular in shape, having sometimes pockets of different sizes and shapes. Thus, the follicles could be classified into two forms, ordinary and acinar. The acinar follicles were further divisible into two parts, a main follicle body and alveolar pockets. The alveolar pockets were the sacs projecting outwards from the wall of the main follicle body. The folliculograms could easily analyze the morphological conditions of the acinar follicles (Table 4).

Between the alveolar pockets or between the main follicle body and alveolar pocket, infoldings were produced. Some of the infoldings contained merely continuations of perifollicular connective tissue and capillaries, others a number of small follicles, and still others a part of just neighboring large or medium-sized follicles. The alveolar pockets were increased in number in proportion to the diameter of the follicles. The frequency of occurrence of acinar follicles varied from case to case even in the same age. Table 4 shows that, in a case of premature birth (corresponding to 32 weeks of prenatal life), all of the follicles examined had no alveolar pockets, while soon after birth some follicles of over 100 μ possessed them. In the 17 years old, a considerable number of follicles over 100 μ became irregular-shaped with a few alveolar pockets, rarely 5. The acinar follicles usually occurred in the peripheral zone of the lobe.

b) Follicular Pattern and Life Periods

A series of quantitative measurements of the follicles indicated that the human thyroid gland appears to change in follicular pattern with increase in age (Figs. 1 to 5). The follicular pattern was conveniently divided into the following 4 types: 1. microfollicular type showing the averaged values of frequencies per mm^2 of follicles in small follicle areas to be above 80 to 100, often above 100 and the maximum values to be between over 100 to 150, sometimes over 150, 2. microfollicular-macrofollicular (or macrofollicular-microfollicular) mixed type — the averaged values to be above 60 to 80 and the maximum values to be above 80 to 100, 3. macrofollicular type — the averaged values to be 40 to 60 and the maximum values to be between above 60 to 80, and 4. transitive macrofollicular type — the averaged values to be 40 to 60 and the maximum values to be above 80 to 100. The values in large follicle areas are not so important in this type of classification method.

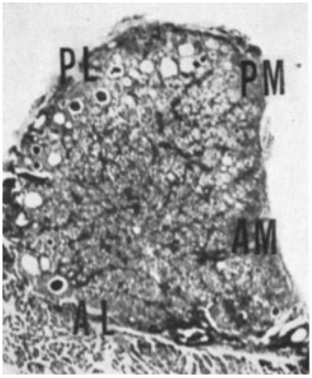

Fig. 6

Fig. 7

Fig. 6. Photomicrograph of a transverse section of the middle part of the lobe. 7 days old male newborn baby. The gland is microfollicular in type. Large follicles are abundantly found in the posterolateral part of the peripheral zone of the lobe. PL: Posterolateral part of the peripheral zone of the lobe; PM: Posteromedial part; AL: Anterolateral part; AM: Anteromedial part and IS: Isthmus. Zenker-formol. Bielschowsky's silver impregnation. × 7

Fig. 7. Photomicrograph of a transverse section of the middle part of the lobe. 2 months old female baby. The gland maintains the same type as that found in Fig. 6. Zenker-formol. Bielschowsky's silver impregnation. × 7

During the newborn period, the thyroid glands were not solid but microfollicular in type, and consisted of exclusively small follicle areas — showing averaged values of 143 to 95 frequencies per mm^2 of follicles (maximum values: 213 to 135 and minimum values: 104 to 55) (Fig. 6). In all of the cases examined large follicle areas were not found. In the peripheral zone of the lobe, large follicles were on the average 327 to 188 μ in the long diameter and 237 to 134 μ in the short diameter (maximum values: 504 to 365 μ in the long diameter # # and 382 to 261 μ in the short diameter #). In the central zone, large follicles showed lower values — averaging 204 to 110 μ in the long diameter and 157 to 77 μ in the short diameter (maximum values: 365 to 139 μ # # and 313 to 104 μ #), and in the isthmus 174 to 139 μ in the long diameter and 121 to 104 μ in the short diameter (maximum values: 226 to 208 μ # # and 174 to 156 μ #). A significant difference in the diameters between the peripheral and central zones was found. The large follicles appeared usually as single elements and rarely in small groups closely packed in the peripheral zone of the lobe and formed small thyromeres with surrounding small follicles (Fig. 6).

During the suckling period the thyroid glands were microfollicular in type and consisted of small follicle areas — showing high averaged values of 160 to 94 frequencies per mm^2 of follicles (maximum values: 180 to 130 and minimum values: 102 to 45) (Fig. 7). Cases where the gland did not contain large follicle areas were 88%. Follicles were still growing. In the peripheral zone of the lobe, especially in its posterolateral and/or posteromedial parts, large follicles grew to an average of 435 to 191 μ in the long diameter and 295 to 156 μ in the short diameter (maximum values: 800 to 295 μ # # and 556 to 226 μ #); in the central zone 243 to 139 μ in the long diameter and 174 to 114 μ in the short diameter (maximum values: 365 to 174 μ # # and 260 to 156 μ #), and in the isthmus 278 to 156 μ in the long diameter and 191 to 104 μ in the short diameter (maximum values: 417 to 243 μ # # and 313 to 174 μ #). In the isthmus, some of the large follicles were greater in diameter than those in the central zone of the lobe. Thyromeres were found only in the peripheral zone of the lobe and remained small in scale.

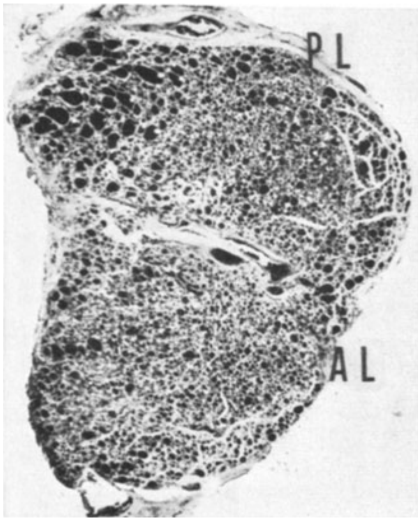

Fig. 8. Photomicrograph of a transverse section of the middle part of the lobe. 3 years old girl (early childhood). Large follicles are abundant in the posterolateral and posteromedial parts of the peripheral zone of the lobe, especially in the transitions between the posterolateral and posteromedial parts, and between the posterolateral and anterolateral parts. The gland maintains the microfollicular type. Zenker-formol. Bielschowsky's silver impregnation. ×7

During early childhood, the thyroid glands were still microfollicular in type and consisted in the major part of small follicle areas with high averaged values of 125 to 82 frequencies per mm^2 of follicles (maximum values: 162 to 119 and minimum values: 88 to 45) (Fig. 8). Cases where the gland did not contain large follicle areas were still frequent (90%). Follicles were growing further. In the peripheral zone of the lobe large follicles showed averaged values of 469 to 243 μ in the long diameter and 348 to 174 μ in the short diameter (maximum values: 922 to 417 μ # # and 609 to 208 μ #), in the central zone 313 to 174 μ in the long diameter and 261 to 121 μ in the short diameter (maximum values: 817 to 243 μ # # and 678 to 191 μ #), and in the isthmus 295 to 174 μ in the long diameter and 226 to 104 μ in the short diameter (maximum values: 539 to 261 μ # # and 400 to 139 μ #). They, singly or in groups, formed thyromeres with surrounding smaller follicles. The thyromeres were prominent in the posterolateral part of the peripheral zone of the lobe, also sometimes in the angle between the anterolateral and anteromedial parts of the peripheral zone (Fig. 8).

During late childhood, the thyroid glands were half microfollicular and half microfollicular-macrofollicular mixed in type and became half-mature consisting of further growing follicles (Figs. 9 and 10). Small follicle areas showed relatively high averaged values of 110 to 53 per mm² of follicles (maximum values: 151 to 69 and minimum values: 68 to 40). Large follicles areas increased in frequency — cases where the gland did not contain large follicle areas abruptly decreased to 56%. Large follicles averaged 574 to 313 μ in the long diameter and 426 to 226 μ in the short diameter (maximum values: 957 to 539 μ ## and 783 to

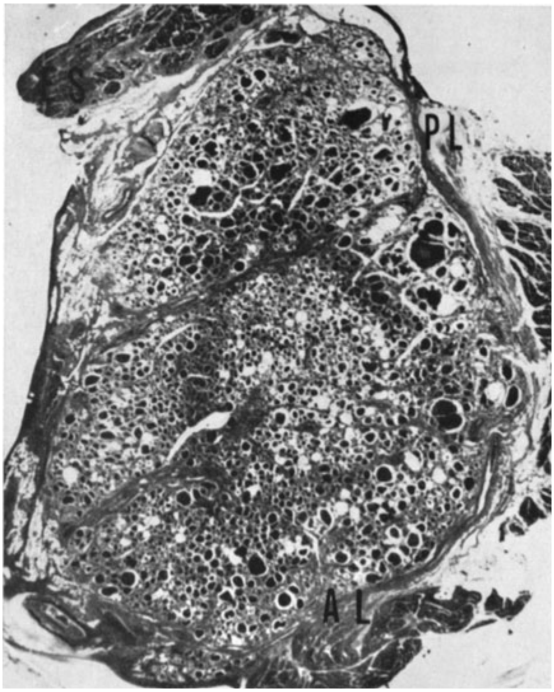

Fig. 9. Photomicrograph of a transverse section of the middle part of the lobe. 10 years old girl (late childhood). The gland begins to change in type from microfollicular type to microfollicular-macrofollicular mixed type. Thyromeres are seen growing in the posterolateral and posteromedial parts of the peripheral zone of the lobe. Primary connective tissue septums are seen. ES: Esophagus. Zenker-formol. Bielschowsky's silver impregnation. × 7

400 μ #) in the peripheral zone of the lobe, 452 to 226 μ in the long diameter and 330 to 156 μ in the short diameter (maximum values: 713 to 330 μ ## and 609 to 261 μ #) in the central zone, and 419 to 226 μ in the long diameter and 295 to 156 μ in the short diameter (maximum values: 922 to 243 μ ## and 643 to 203 μ #) in the isthmus. Thyromeres were found in the same zone as in previous periods (Figs. 9 and 10). Bands and islets consisting of numerous very small follicles became prominent just beneath the capsule as growth of general follicles progressed (Figs. 9 and 10).

During puberty the thyroid glands were half-mature — microfollicular-macrofollicular mixed in type and still contained further growing follicles (Fig. 11). Small follicle areas showed far lower averaged values of 86 to 60 frequencies per mm² of follicles (maximum values: 120 to 99 and minimum values: 56 to 40), while large follicle areas indicated averaged values of 29 to 34 and were found in all of the cases examined. Large follicles averaged 661 to 405 μ in the long diameter and 435 to 296 μ in the short diameter (maximum values: 1078 to 556 μ ## and 991 to 400 μ #) in the peripheral zone of the lobe, and 504 to 324 μ in the long diameter and 348 to 226 μ in the short diameter (maximum values: 939 to 522 μ ## and 522 to 417 μ #) in the central zone. A significant difference in the diameters between the peripheral and central zones was maintained. In the isthmus they averaged 435 to 330 μ in the long diameter and 313

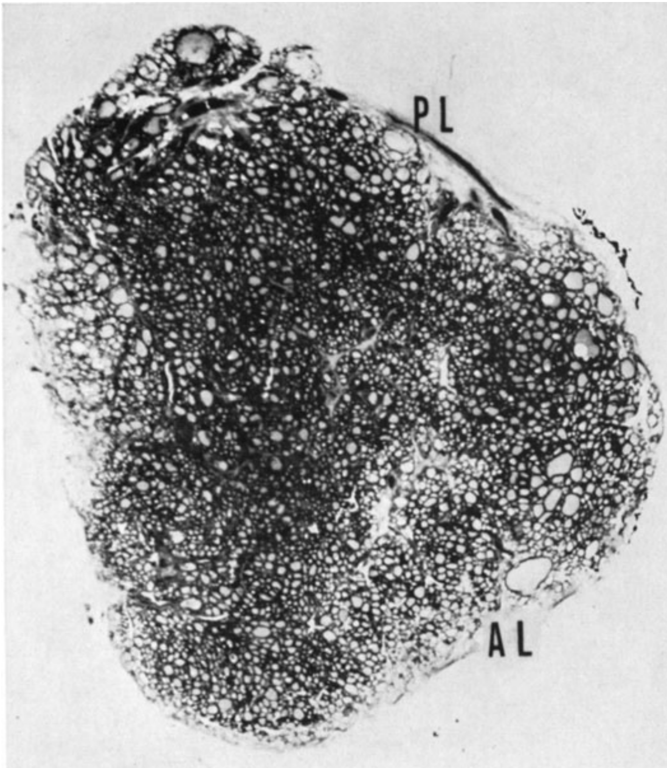

Fig. 10. Photomicrograph of a transverse section of the middle part of the lobe. 12 years old girl (late childhood). The gland is seen changing from microfollicular type to microfollicular-macrofollicular type. Thyromeres are seen growing in the peripheral zone. Formol. Hematoxylin and eosin. × 7

to 226 μ in the short diameter (maximum values: 574 to 556 μ ## and 522 to 295 μ #). These large follicles, in groups of 2 to 25, average 5, began to produce thyromeres of large scale, together with surrounding smaller follicles. Bands and islets consisting of numerous very small follicles were found just beneath the capsule. No other changes specific to puberty occurred in follicles.

During early adult life, a new trend marked by rapidly accelerated growth of the follicles, set in and persisted. In the beginning stage (16 to 19 years old) the thyroid glands became almost completely mature but were half microfollicular-macrofollicular mixed in type and half macrofollicular (Fig. 12). Small follicle areas showed lower averaged values of 77 to 45 (maximum values: 106 to 58 and minimum values: 55 to 40) frequencies per mm² of follicles. Large follicle areas were found in all of the cases examined and increased not only in the peripheral zone of the lobe but also in the central zone and further in the isthmus. They showed averaged values of 35 to 17 frequencies per mm² of follicles. Large follicles

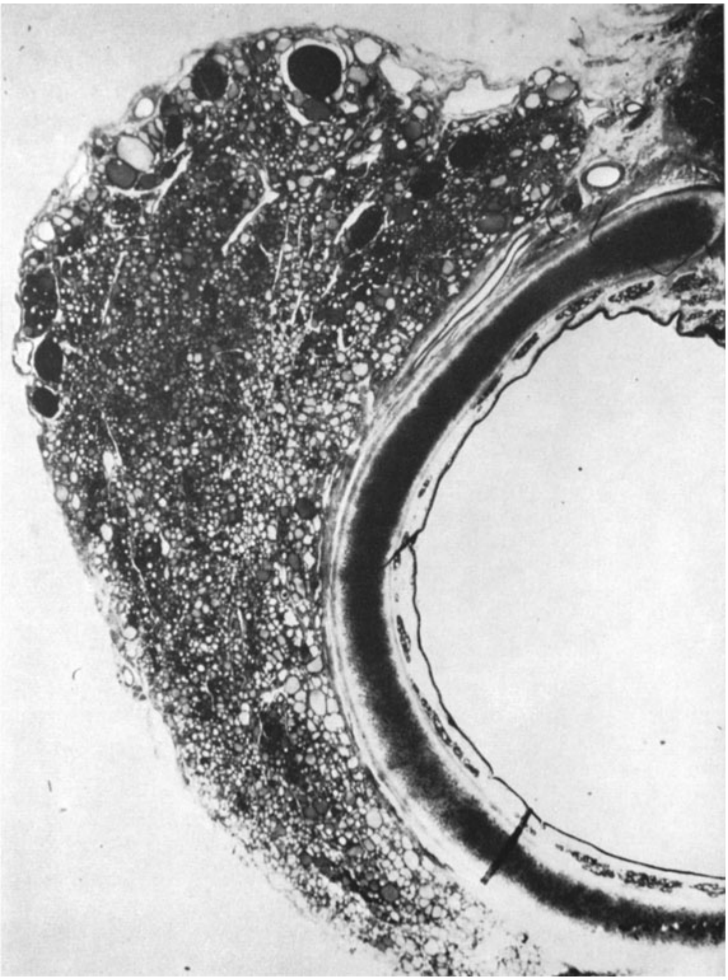

Fig. 11. Photomicrograph of a transverse section of the middle part of the lobe with the isthmus. 15 years old boy (puberty). The gland is changed to microfollicular-macrofollicular type. Thyromeres and large follicles are abundant in the posterolateral and posteromedial parts of the peripheral zone of the lobe. Formol. Hematoxylin and eosin. × 7

increased in size showing highest averaged values of 738 to 452 μ in the long diameter and 499 to 310 μ in the short diameter (maximum values: 1350 to 591 μ # # and 1131 to 452 μ #) in the peripheral zone of the lobe and 780 to 303 μ in the long diameter and 574 to 278 μ in the short diameter (maximum values: 1392 to 435 μ # # and 1218 to 417 μ #) in the central zone. A significant difference in the diameters between the two zones was maintained in the same manner as in previous stages (Fig. 2). In the isthmus, large follicle were 504 to

348 μ in the long diameter and 365 to 261 μ in the short diameter (maximum values: 626 to 417 μ # # and 504 to 400 μ #).

In the late stage (20 to 24 years old), the thyroid glands attained complete maturity in structure and were generally macrofollicular in type (Fig. 13). Small

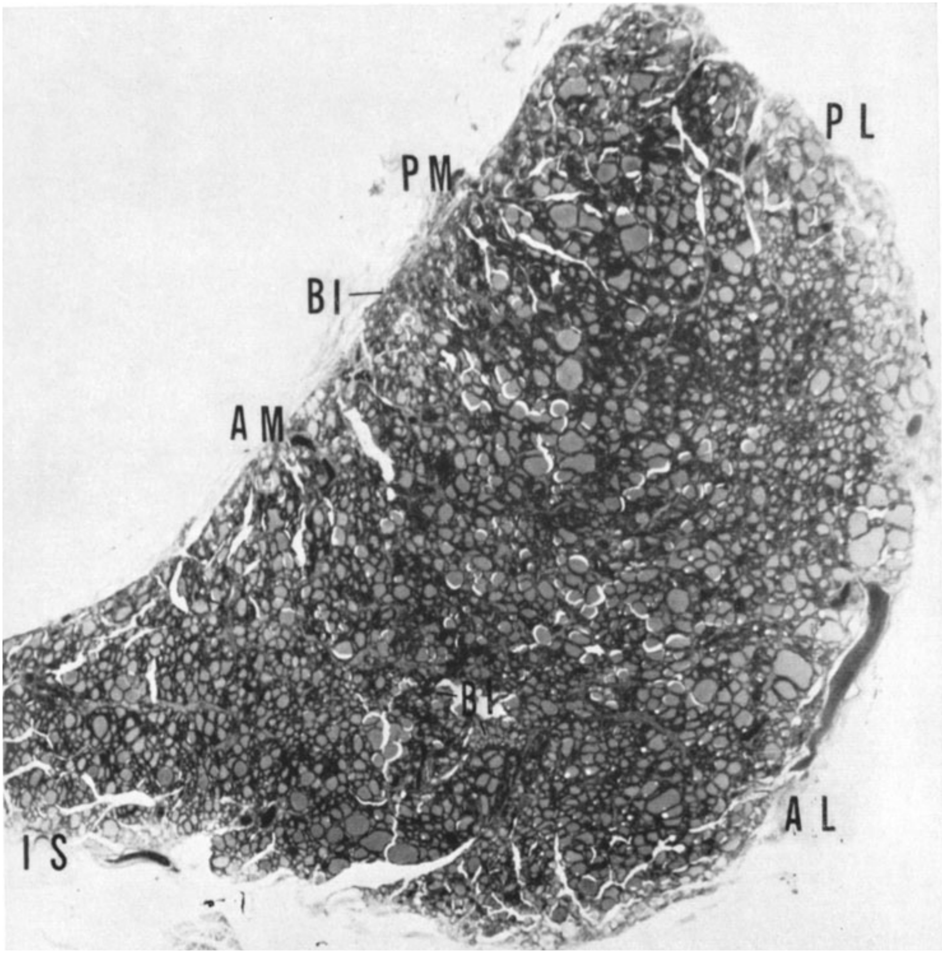

Fig. 12. Photomicrograph of a transverse section of the middle part of the lobe with the isthmus. 19 years old woman (beginning stage of early adult life). The gland is macrofollicular in type. Thyromeres are well grown in the posterolateral and posteromedial parts of the peripheral zone of the lobe and in the posterior half of the central zone. BI: Band and islets consisting of numerous very small follicles. Formol. Hematoxylin and eosin. × 7

follicle areas showed lowest averaged values of 67 to 45 (maximum values: 93 to 53 and minimum values: 49 to 40) frequencies per mm^2 of follicles while those of large follicle areas were 37 to 20 and were found in all of the cases examined. The averaged and maximum values of the small follicle areas approximated the values of the large follicle areas (Fig. 1). Large follicles maintained highest levels in diameters — average 748 to 330 μ in the long diameter and 556 to 243 μ in the short diameter (maximum values: 1165 to 556 μ # # and 957 to 348 μ #) in the peripheral zone of the lobe and 626 to 278 μ in the long diameter and 435 to

208 μ in the short diameter (maximum values: 904 to 417 μ # # and 835 to 278 μ #) in the central zone. In the isthmus they averaged 504 to 261 μ in the long diameter and 330 to 174 μ in the short diameter (maximum values: 852 to

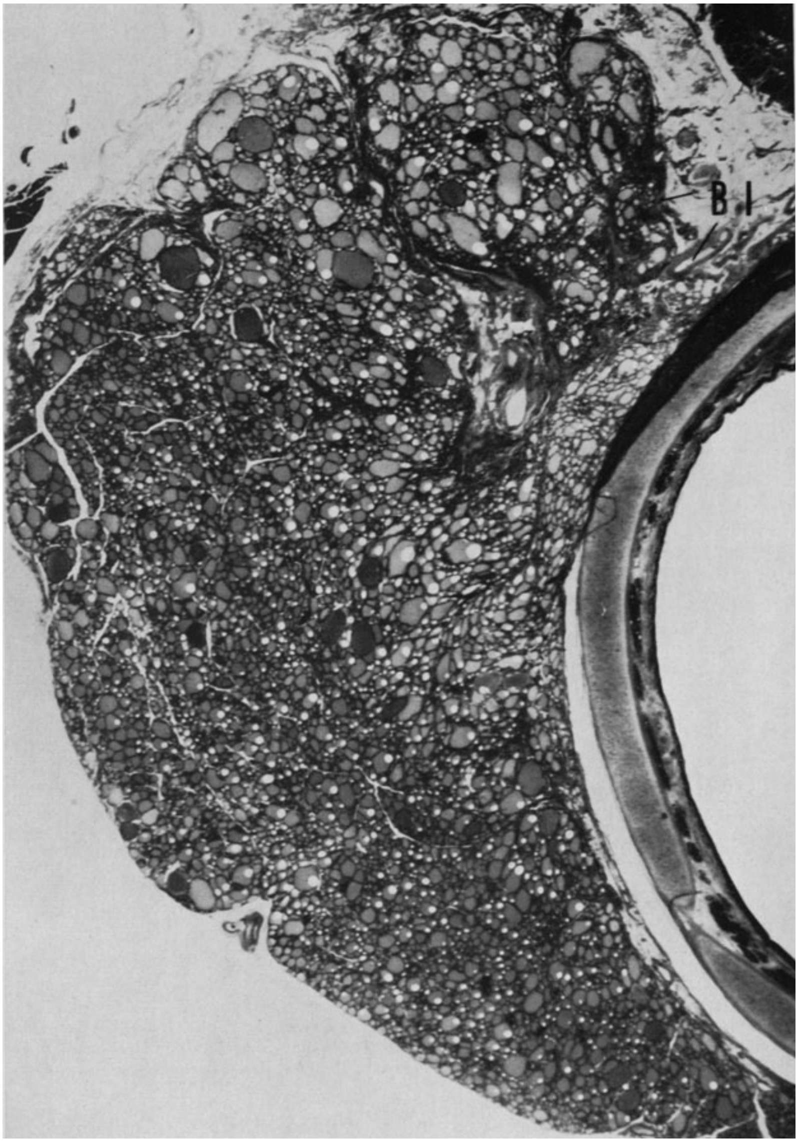

Fig. 13. Photomicrograph of a transverse section of the middle part of the lobe with the isthmus. 23 years old man (late stage of early adult life). The gland is macrofollicular. Thyromeres has grown further in the same parts as those in fig. 12. Bands and islets consisting of very small and small follicles (BI) are found in the posterolateral and posteromedial parts of the peripheral zone of the lobe. Formol. Hematoxylin and eosin. × 7

348 μ # # and 539 to 243 μ #). Surrounded by a layer of smaller follicles, these large follicles, singly or in groups of 5 (two to 12), formed thyromeres. Just beneath the capsule, bands and islets consisting of very small follicles were found.

During the beginning stage (25 to 29 years old) of late adult life, the thyroid glands maintained their fully grown structure (Fig. 14), but showed slightly higher averaged values of 87 to 45 frequencies per mm^2 of follicles (maximum

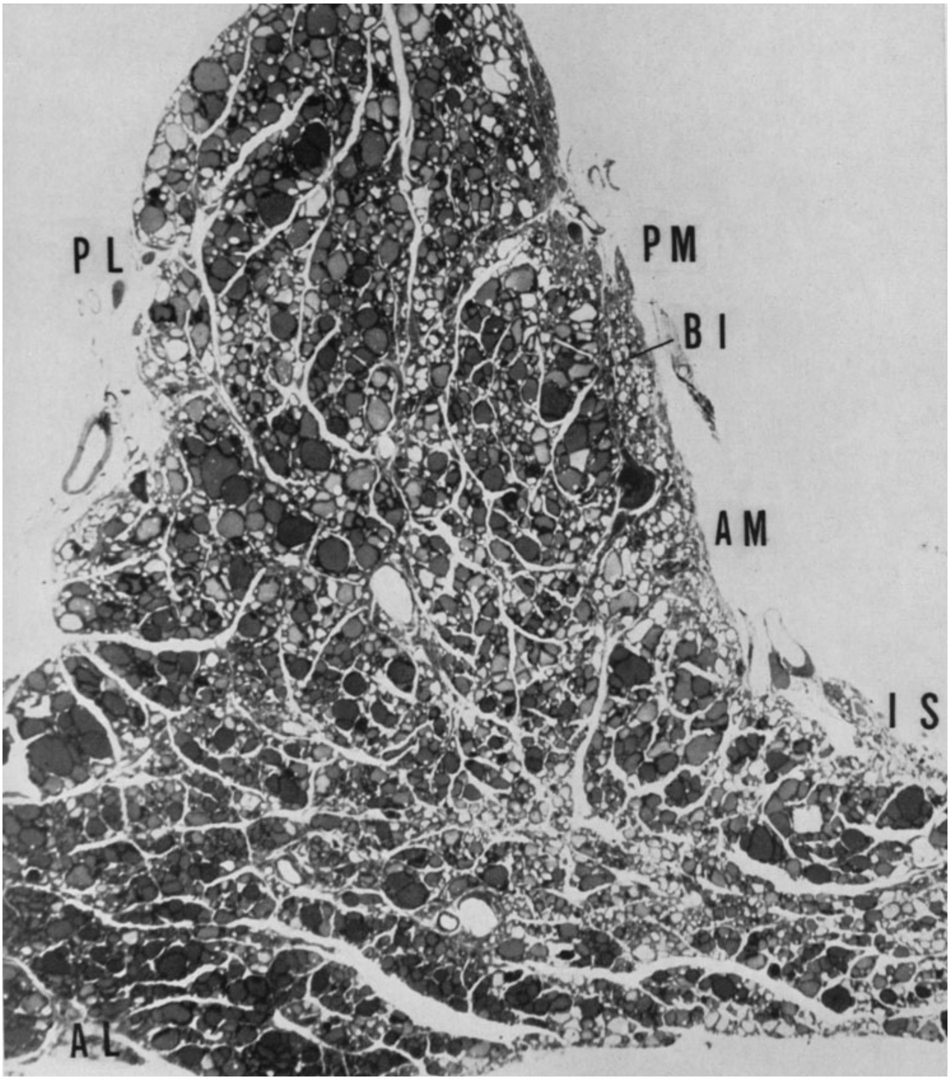

Fig. 14. Photomicrograph of a transverse section of the middle part of the lobe with the isthmus. 27 years old man (beginning stage of late adult life). The gland is fully macrofollicular. Thyromeres mature and are abundant in the same parts of the lobe. Bands and islets consisting of very small and small follicles are seen in the same parts as those in fig. 13. Formol. Hematoxylin and eosin. × 7

values: 99 to 52, exceptionally 142 and minimum values: 47 to 40) in small follicle areas. Large follicle areas averaged 38 to 28. The glands were held in readiness to change in follicular pattern. Cases where the gland did not contain large follicle areas began to appear again and were 10% in proportion. Large follicles averaged 800 to 261 μ in the long diameter and 504 to 191 μ in the short diameter

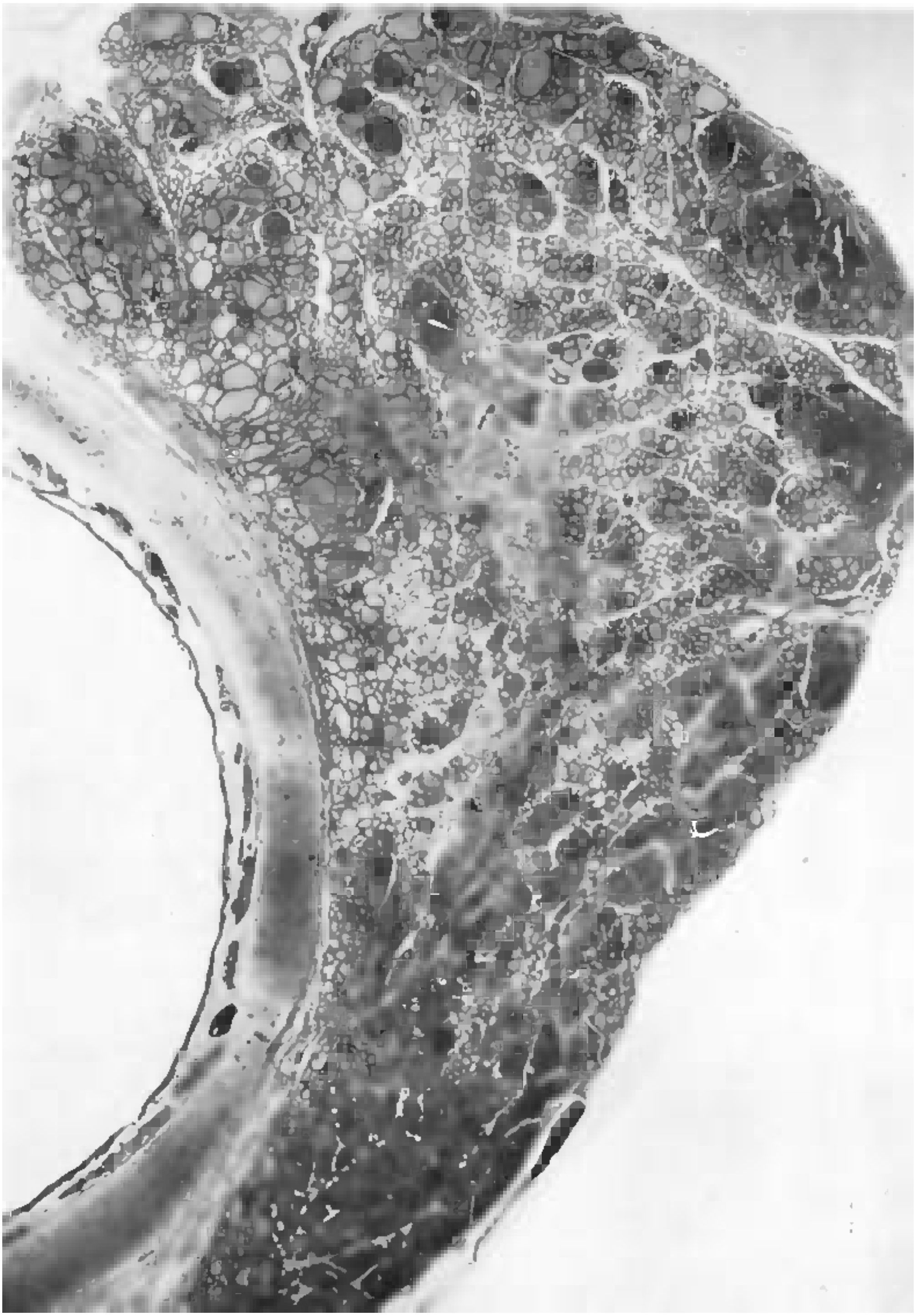

Fig. 15. Photomicrograph of a transverse section of the middle part of the lobe with the isthmus. 31 years old man (middle stage of late adult life). The gland remains fully macrofollicular. Thyromeres, and bands and islets of very small and small follicles are found in the same parts as those found in earlier stages. Formol. Hematoxylin and eosin. × 7

(maximum values: 1566 to 417 μ # # and 870 to 261 μ #) in the peripheral zone of the lobe, and 626 to 261 μ in the long diameter and 452 to 191 μ in the short diameter (maximum values: 1131 to 348 μ # # and 870 to 278 μ #) in the central zone. In the isthmus, they averaged 469 to 295 μ in the long diameter and

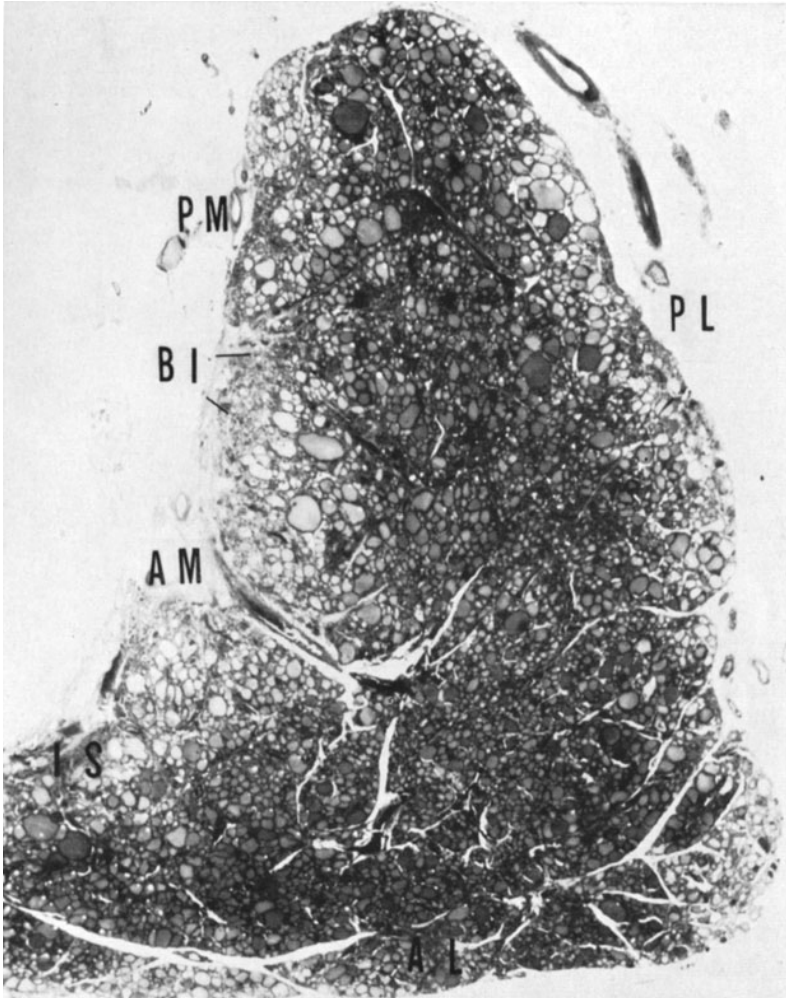

Fig. 16. Photomicrograph of a transverse section of the middle part of the lobe with the isthmus. 36 years old man (middle stage of late adult life). The gland is seen growing downwards — changing to macrofollicular-microfollicular type. Thyromeres are smaller in scale. Bands and islets of very small small follicles become outstanding in the same parts as those found in earlier stages. Formol. Hematoxylin and eosin. × 7

348 to 174 μ in the short diameter (maximum values: 1270 to 435 μ # # and 835 to 313 μ #). They, singly or in groups of 5 to 7, together with surrounding smaller follicles, formed thyromeres.

During the middle stage (30 to 39 years old), the thyroid glands became variable in type and were half macrofollicular or transitive macrofollicular and half macrofollicular-microfollicular mixed in type (Figs. 15 and 16). A reversed trend began to occur (Fig. 1). Small follicle areas increased, with averaged values of 87 to 43 (maximum values: 120 to 54 and minimum values: 54 to 40). The averaged and maximum values of the small follicle areas began to separate from each other and further from the same values of the large follicle areas. Cases where the gland did not contain large follicle areas slightly increased in proportion (15%). Large follicles averaged 775 to 310 μ in the long diameter and 574 to 208 μ in the short diameter (maximum values: 1966 to 469 μ # # and 1409 to 313 μ #) in the peripheral zone of the lobe and 591 to 291 μ in the long diameter and 469 to 208 μ in the short diameter (maximum values: 922 to 417 μ # # and 870 to 261 μ #) in the central zone. The previous difference in the diameters between the peripheral and central large follicles was decreasing. In the isthmus, they averaged 591 to 291 μ in the long diameter and 539 to 156 μ in the short diameter (maximum values: 904 to 400 μ # # and 783 to 208 μ #). Thyromeres and bands of very small follicles remained in the same state as found in previous stages.

During the late stage (40 to 44 years old), the thyroid glands remained variable in type and were still half transitive macrofollicular and half macrofollicular-microfollicular mixed in type, and showed averaged values of 81 to 45 (maximum values: 125 to 55 and minimum values: 48 to 40) frequencies per mm^2 of follicles in small follicle areas and 36 to 30 in large follicle areas. Cases where the gland did not contain large follicle areas were still relatively rare (14% in proportion). Large follicles averaged 696 to 313 μ in the long diameter and 487 to 243 μ in the short diameter (maximum values: 1096 to 417 μ # # and 487 to 243 μ #) in the peripheral zone of the lobe, and 626 to 330 μ in the long diameter and 469 to 243 μ in the short diameter (maximum values: 1009 to 382 μ # # and 870 to 295 μ #) in the central zone. In this stage there occurred a new trend for the peripheral large follicles to begin decreasing significantly in diameter and approach the values near by the central large follicles (Fig. 2). In the isthmus they averaged 469 to 169 μ in the long diameter and 330 to 208 μ in the short diameter (maximum values: 818 to 365 μ # # and 556 to 278 μ #). They formed thyromeres, singly or in groups of 5 or 6 with surrounding smaller follicles. The thyromeres placed peripherally began to resemble in scale those placed centrally.

During the presenium, the thyroid glands became macrofollicular-microfollicular mixed in type, with a tendency to change to the microfollicular type (Fig. 17). The thyroid glands showed further more increase with averaged values of 107 to 49 (maximum values: 145 to 59 and minimum values: 68 to 41) frequencies per mm^2 of follicles in small follicle areas. The averaged and maximum values separated further from each other and from the values of large follicle areas (Fig. 1). Large follicle areas were averaged at 38 to 31. Cases where the gland did not contain large follicle areas increased abruptly to 50% in proportion. Large follicles decreased slightly in diameter and averaged 539 to 261 μ in the long diameter and 382 to 156 μ in the short diameter (maximum values: 1009 to 400 μ # # and 643 to 243 μ #) in the peripheral zone of the lobe, and 539 to 261 μ in the long diameter and 382 to 174 μ in the short diameter (maximum values: 1131 to 435 μ # # and 904 to 226 μ #) in the central zone. In the isthmus they averaged 522 to 208 μ in the long diameter and 365 to 156 μ in the short diameter (maximum values: 957 to 330 μ # # and 574 to 243 μ #). The large follicles, singly or in groups of about 5 with surrounding smaller follicles, formed thyromeres. Bands and islets of numerous very small and small follicles became prominent.

During the early stage of the senium (50 to 59 years old), the thyroid glands became almost regressively microfollicular but partly remained macrofollicular-

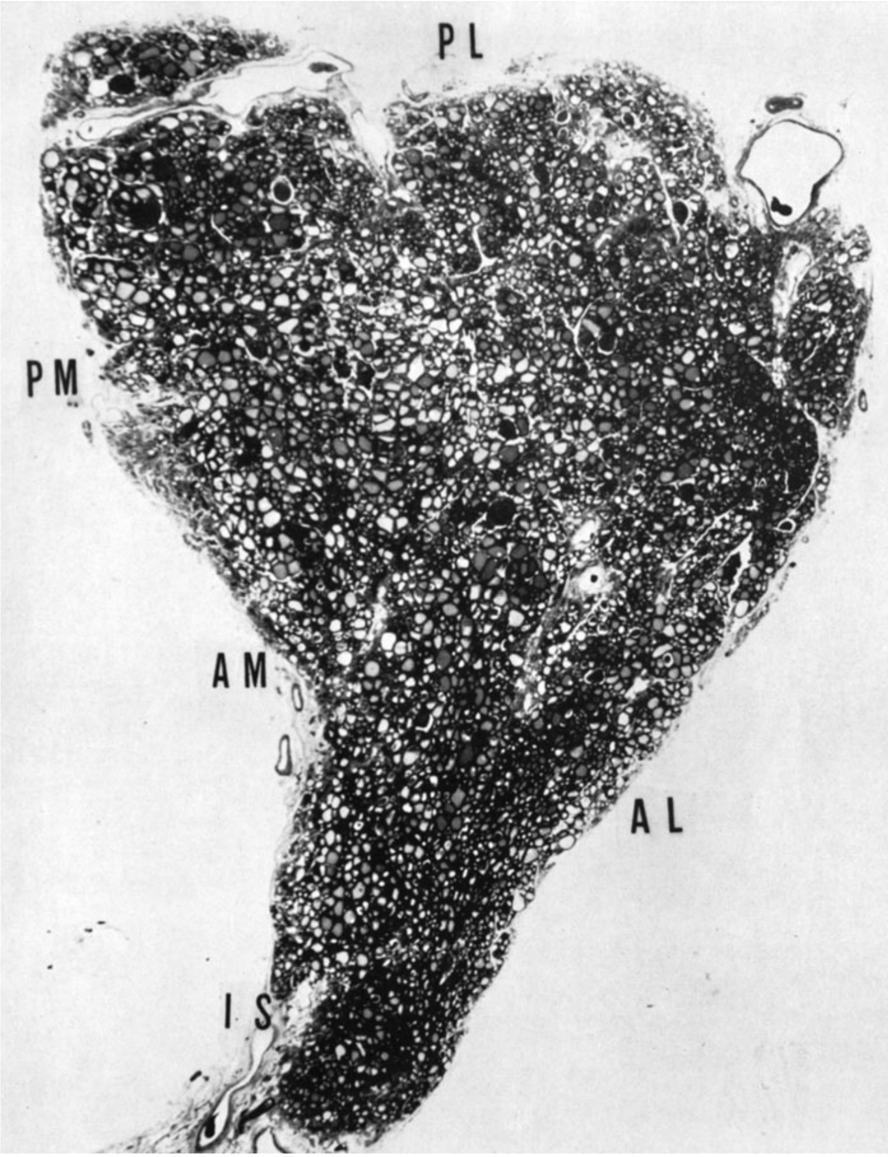

Fig. 17. Photomicrograph of a transverse section of the middle part of the lobe with the isthmus. 46 years old man (presenium). The gland is macrofollicular-microfollicular mixed type. Formol. Hematoxylin and eosin. × 7

microfollicular mixed in type (Fig. 18), showing high averaged values of 125 to 81 and exceptionally 47 (maximum values: 170 to 68 and minimum values: 92 to 41) frequencies per mm^2 of follicles in small follicle areas. Large follicle areas were on the average between 38 and 21. Cases where the gland did not contain large follicle areas increased to 61% in proportion. Large follicles decreased further in diameter and averaged 552 to 208 μ in the long diameter and 364 to

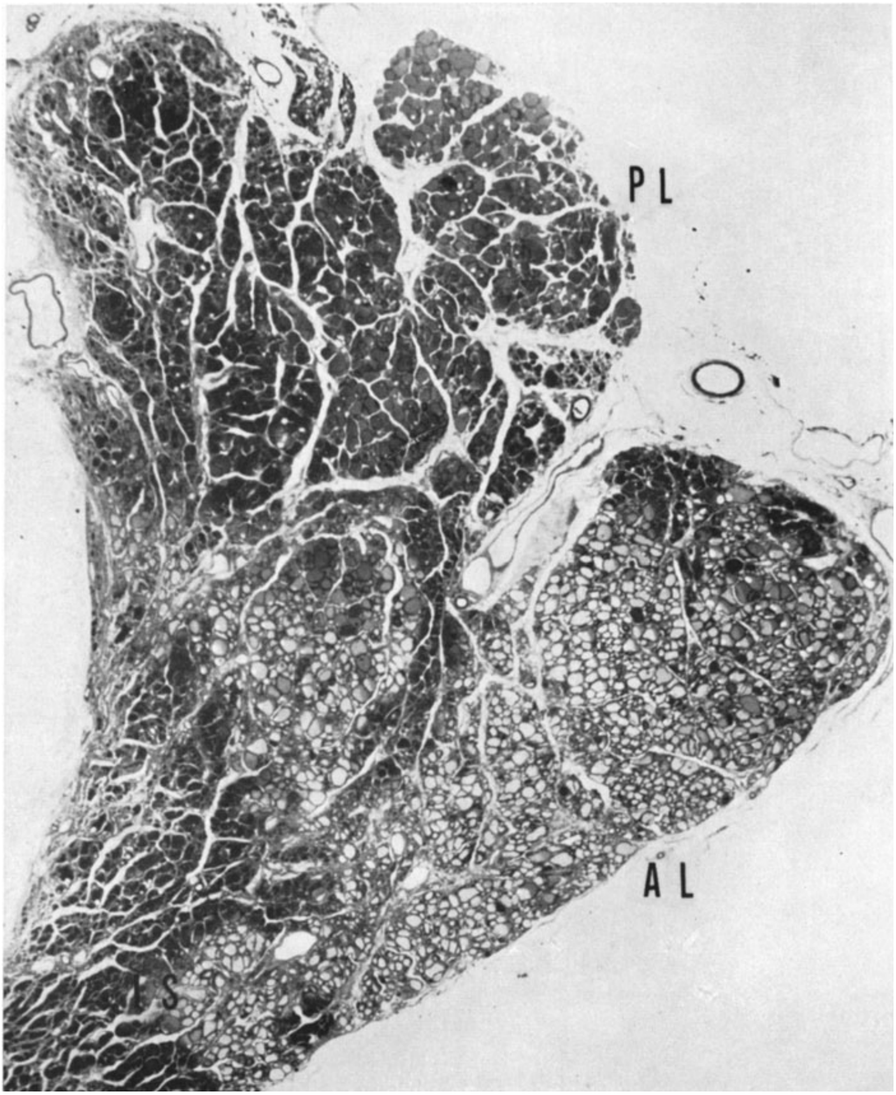

Fig. 18. Photomicrograph of a transverse section of the middle part of the lobe with the isthmus. 55 years old man (beginning stage of the senium). The gland still remains macrofollicular-microfollicular mixed in type. Formol. Hematoxylin and eosin. × 7

139 μ in the short diameter (maximum values: 1131 to 295 μ # # and 591 to 226 μ #) in the peripheral zone of the lobe, and 522 to 191 μ in the long diameter and 400 to 121 μ in the short diameter (maximum values: 1009 to 295 μ # # and 556 to 208 μ #) in the central zone. In the isthmus they averaged 609 to 156 μ in the long diameter and 295 to 52 μ in the short diameter (maximum values:

835 to 174 μ # # and 452 to 139 μ #). The large follicles, singly or in groups with surrounding small follicles, formed thyromeres of small size. Bands and islets consisting of many very small follicles were found just beneath the capsule.

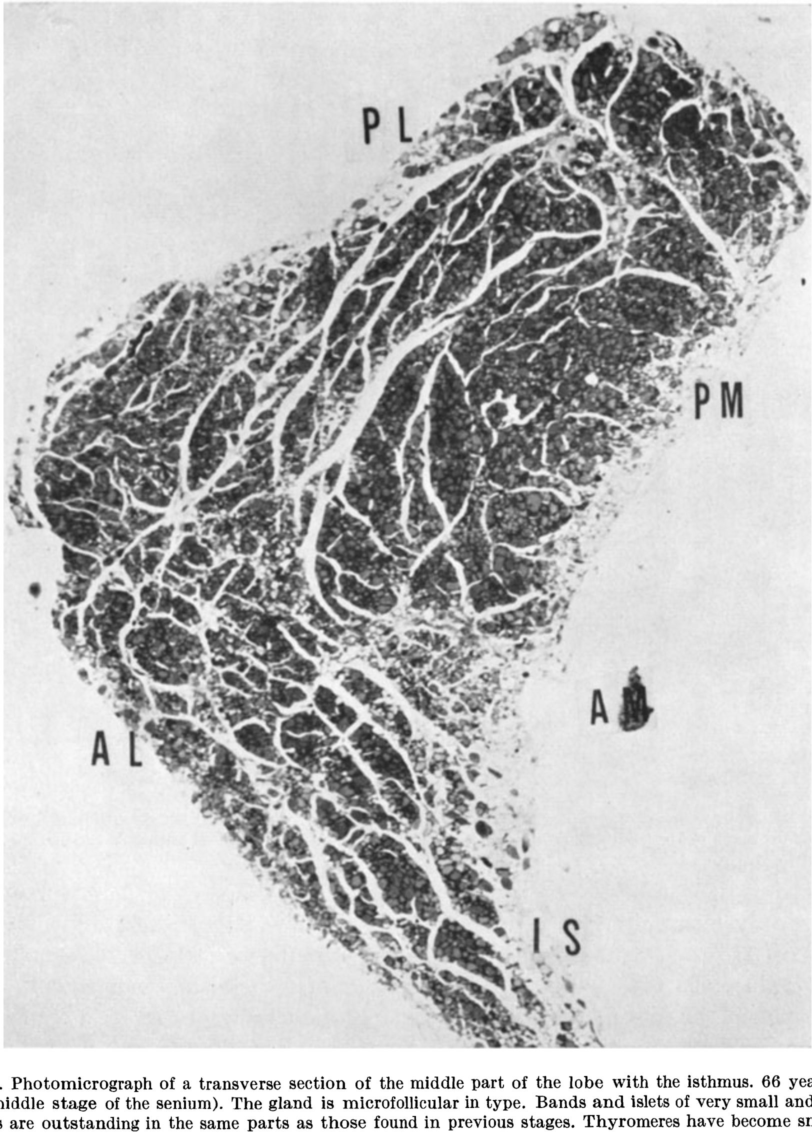

Fig. 19. Photomicrograph of a transverse section of the middle part of the lobe with the isthmus. 66 years old man (middle stage of the senium). The gland is microfollicular in type. Bands and islets of very small and small follicles are outstanding in the same parts as those found in previous stages. Thyromeres have become small in scale. Formol. Hematoxylin and eosin. × 7

During the middle stage (60 to 69 years old), the thyroid glands became regressively microfollicular in type (Fig. 19) and showed almost the same averaged values of 113 to 80 and exceptionally 53 (maximum values: 160 to 75 and minimum values: 86 to 40) frequencies per mm^2 of follicles in small follicle areas. Large follicle areas showed also almost the same values as those found in the early stage. Cases where the gland did not contain large follicle areas increased to 68%.

Large follicles averaged 656 to 156 μ in the long diameter and 435 to 121 μ in the short diameter (maximum values: 1305 to 313 μ # # and 800 to 243 μ #) in the peripheral zone of the lobe, and 574 to 139 μ in the long diameter and 435 to 104 μ in the short diameter (maximum values: 992 to 191 μ # # and 783 to 156 μ #) in the central zone. In the isthmus they averaged 661 to 156 μ in the long diameter and 452 to 121 μ in the short diameter (maximum values: 1131 to 208 μ # # and 696 to 174 μ #). Bands and islets of numerous very small follicles were found just beneath the capsule.

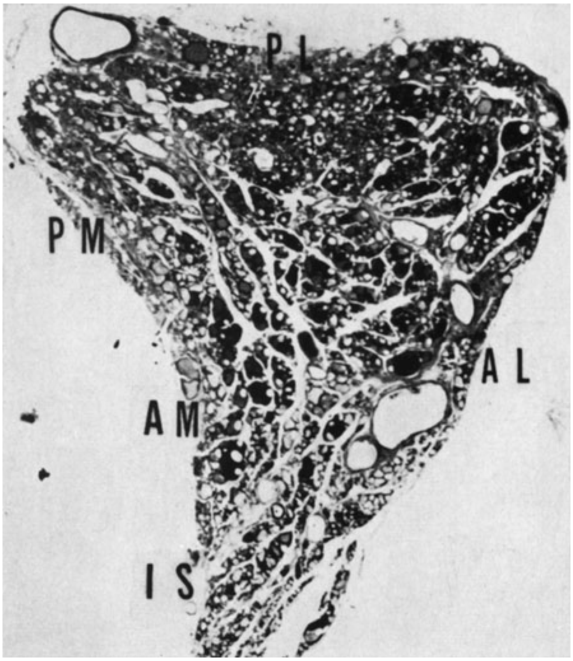

Fig. 20. Photomicrograph of a transverse section of the middle part of the lobe with the isthmus. 83 years old woman (late stage of the senium). The gland is microfollicular in type. Formol. Hematoxylin and eosin. × 7

During the late stage (seventies and eighties), the thyroid glands remained regressively microfollicular in type. In the seventies they showed high averaged values of 114 to 83 and exceptionally 58 (maximum values: 178 to 79 and minimum values: 98 to 40) frequencies per mm² of follicles in small follicle areas. Cases where the gland did not contain large follicle areas further increased to 77% in proportion. Large follicles averaged 469 to 226 μ in the long diameter and 348 to 121 μ in the short diameter (maximum values: 870 to 348 μ # # and 661 to 191 μ #) in the peripheral zone of the lobe and 487 to 191 μ in the long diameter and 330 to 156 μ in the short diameter (maximum values: 904 to 330 μ # # and 643 to 243 μ #) in the central zone. No significant difference in the diameters between the peripheral and central large follicles was found and their relation was rather reversed. In the isthmus they averaged 435 to 191 μ in the long diameter and 278 to 87 μ in the short diameter (maximum values: 1044 to 278 μ # # and 417 to 156 μ #). Exceptionally large follicles of over 1000 μ remained sometimes as cysts not only in the peripheral zone of the lobe but also in the central zone and in the isthmus. Thyromeres of smaller size were formed in the same manner as in previous stages. Bands and islets of numerous very small and small follicles were also found.

In the eighties, the thyroid glands showed far increased regression (Fig. 20), with high averaged values of 121 to 89 and exceptionally 67 (maximum values: 188 to 104 and minimum values: 97 to 40) frequencies per mm² of follicles in small follicle areas. Cases where the gland did not contain large follicle areas further increased to 90% in proportion. Large follicles averaged 452 to 208 μ in the long diameter and 330 to 113 μ in the short diameter (maximum values: 784 to 313 μ ## and 539 to 226 μ #) in the peripheral zone of the lobe and 539 to 191 μ in the long diameter and 400 to 139 μ in the short diameter (maximum values: 991 to 278 μ ## and 696 to 191 μ #) in the central zone. The same situation as to the peripheral and central large follicles as that found in the seventies was seen (Fig. 20). In the isthmus they averaged 382 to 139 μ in the long diameter and 243 to 104 μ in the short diameter (maximum values: 817 to 191 μ ## and 452 to 139 μ #). The large follicles, singly or in groups, together with surrounding small follicles formed thyromeres of small size. Bands and islets of numerous very small follicles were found just beneath the capsule, especially in its medial part.

c) Sex Difference

Comparison of the follicular patterns between man and woman — the averaged diameters of the large follicles found in the peripheral and central zones of the lobe and the averaged frequencies per mm² of follicles in the small follicle areas was computed in the 44 age groups (Table 6). Although the cases compared were statistically small in number and not sufficient to demonstrate definitely a difference between both sexes (Table 1), some trend may be seen. Already before puberty, the difference — the follicles were somewhat larger in man than in woman — was relatively definite and was main-

Table 5. *Frequencies of occurrence of Sanderson-Damberg's bolster-like swellings of the follicle wall and their relatives in different periods of life*

Periods	Age in years	No. of cases examined			No. of cases where Sanderson-Damberg's swellings and their relatives occur					
					Sanderson-Damberg's swellings ##		Their relatives #		## and #	
		man	woman	total	man	woman	man	woman	man	woman
Birth to childhood	0—12	23	23	46	2 (8%)	1 (4%)	—	—	2 (8%)	1 (4%)
Puberty	13—15	2	1	3	—	—	—	—	—	—
Early adult life	16—24	24	12	36	1 (4%)	2 (16%)	2 (8%)	2 (16%)	3 (12%)	4 (32%)
Late adult life	25—44	68	12	80	8 (11%)	2 (16%)	2 (2%)	1 (8%)	10 (13%)	3 (24%)
Presenium	45—49	20	4	24	6 (30%)	—	2 (10%)	—	8 (40%)	—
Senium	50—88	101	36	137	22 (21%)	6 (16%)	—	—	22 (21%)	6 (16%)
Throughout life		238	88	326	39 (16%)	11 (12%)	6 (2%)	3 (3%)	45 (18%)	14 (15%)

Tabele 6. *Comparison between the follicle patterns of man and woman in the human thyroid gland*

Age in years	Sex	No. of cases	Large Follicles				Frequencies/mm² of follicles in small follicle areas
			Peripheral		Central		
			long diameter μ	short diameter μ	long diameter μ	short diameter μ	
3	men	1	418	330	313	261	98
	women	1	313	208	226	156	101**
6	men	3	440 (452—417)	301 (331—261)	266 (330—208)	185 (191—174)	97 (105—88)
	women	2	410 (472—348)	305 (368—243)	277 (329—226)	204 (252—156)	95 (110—80)
8	men	1	574	382	348	261	80
	women	2	408 (417—400)	295 (313—278)	286 (295—278)	199 (208—191)	99 (108—91) **
9	men	2	519 (569—469)	378 (426—330)	327 (348—306)	242 (261—223)	91 (92—91)
	women	1	452	278	313	243	97**
12	men	3	492 (504—469)	347 (365—313)	405 (452—382)	306 (330—295)	64 (72—53)
	women	1	417	278	295	226	78**
16	men	1	468	310	404	278	50
	women	2	530 (609—452)	350 (382—318)	435 (522—348)	313 (365—261)	66 (77—55)
17	men	1	539	365	487	365	50
	women	2	596 (683—510)	401 (426—376)	388 (473—303)	305 (329—282)	65 (77—53)*
18	men	1	574	469	435	348	52
	women	1	487	313	365	243	56**
19	men	2	664 (738—591)	458 (499—417)	668 (780—556)	478 (574—382)	47 (50—45)
	women	3	527 (574—487)	388 (417—365)	440 (452—435)	330 (330—330)	51 (55—46) **
20	men	4	486 (748—330)	356 (556—243)	391 (522—278)	312 (365—208)	58 (67—52)
	women	1	435	313	400	295	51*
21	men	6	555 (626—507)	419 (487—366)	481 (626—388)	399 (435—300)	52 (61—48)
	women	1	469	313	382	278	53**
22	men	2	573 (643—504)	365 (417—313)	461 (487—435)	308 (382—243)	42 (50—45)
	women	1	487	365	435	348	55*
25	men	7	569 (800—435)	377 (504—295)	462 (626—348)	325 (452—243)	51 (58—47)
	women	1	417	278	295	226	62**
27	men	5	546 (678—417)	388 (469—261)	454 (504—382)	319 (382—278)	51 (65—45)
	women	2	582 (678—487)	382 (469—295)	486 (556—417)	330 (365—295)	58 (59—58)
28	men	5	510 (696—376)	360 (452—273)	435 (522—331)	302 (382—227)	60 (87—50)
	women	1	452	278	452	400	55
31	men	5	587 (696—435)	410 (522—261)	483 (556—330)	340 (417—226)	58 (65—48)
	women	3	417 (452—382)	278 (295—261)	382 (400—365)	226 (278—261)	61 (64—59)*
36	men	1	469	313	539	400	69
	women	1	330	226	295	208	75**
38	men	3	459 (578—382)	346 (432—295)	406 (470—365)	309 (390—261)	54 (70—43)
	women	1	661	435	522	365	53
39	men	5	470 (539—386)	316 (348—261)	426 (522—338)	308 (348—270)	58 (64—53)
	women	2	356 (365—348)	239 (243—235)	356 (400—313)	269 (295—243)	67 (75—59)*
41	men	3	574 (696—504)	394 (487—348)	510 (626—417)	382 (469—261)	62 (81—45)
	women	1	400	295	330	243	71**
46	men	2	338 (382—295)	243 (295—191)	356 (382—330)	243 (295—191)	72 (73—71)
	women	3	318 (365—278)	220 (243—174)	295 (330—278)	208 (226—191)	73 (89—64)*
49	men	2	452 (469—435)	303 (329—278)	368 (423—313)	245 (271—208)	63 (64—63)
	women	1	278	156	261	174	103**
50	men	3	440 (538—348)	309 (329—278)	368 (423—313)	245 (282—208)	63 (77—52)
	women	1	382	243	348	243	56*
51	men	4	401 (528—295)	276 (341—226)	354 (410—261)	257 (298—208)	78 (92—67)
	women	1	313	243	295	243	87*
54	men	1	339	240	320	191	59
	women	1	504	295	382	278	96
55	men	6	375 (487—278)	240 (330—156)	365 (522—243)	278 (400—139)	77 (105—54)
	women	1	275	204	271	188	61
56	men	2	426 (504—348)	251 (295—208)	391 (469—313)	269 (313—226)	81 (87—76)
	women	1	552	204	271	188	61*
57	men	9	375 (504—282)	248 (313—187)	347 (452—283)	244 (313—226)	82 (98—53)
	women	1	348	226	348	208	92*
60	men	2	338 (382—295)	226 (278—174)	339 (400—278)	234 (295—174)	89 (101—77)
	women	1	295	191	278	208	97**
61	men	4	421 (469—382)	295 (313—261)	373 (417—313)	291 (400—208)	77 (88—60)
	women	1	243	156	226	156	103**
63	men	4	417 (626—295)	260 (365—191)	391 (574—295)	273 (400—171)	78 (99—60)
	women	1	452	295	417	295	80

Table 6 (continued)

Age in years	Sex	No. of cases	Large Follicles				Frequencies/mm² of follicles in small follicle areas
			Peripheral		Central		
			long diameter μ	short diameter μ	long diameter μ	short diameter μ	
67	men	3	450 (656—330)	265 (278—243)	329 (365—313)	254 (162—243)	89 (98—77)
	women	1	313	226	313	243	95**
70	men	1	348	226	330	261	74
	women	2	313 (365—261)	226 (261—191)	321 (365—278)	234 (261—208)	92 (96—89)*
72	men	3	341 (382—365)	241 (273—208)	353 (382—313)	234 (261—208)	90 (94—85)
	women	2	373 (382—365)	252 (278—226)	325 (348—313)	234 (243—226)	89 (94—84)
74	men	3	385 (452—257)	275 (348—183)	391 (487—271)	273 (330—211)	69 (89—60)
	women	2	417 (452—382)	278 (295—261)	403 (452—365)	295 (330—261)	73 (83—64)
76	men	1	413	226	278	208	114
	women	3	359 (469—278)	254 (330—191)	324 (365—278)	245 (295—208)	94 (108—87)
77	men	1	295	208	278	208	107
	women	1	295	208	191	156	111**
78	men	1	295	208	313	174	90
	women	1	313	208	295	191	100
80	men	1	348	208	278	208	203
	women	2	374 (435—313)	260 (313—208)	339 (400—278)	243 (295—191)	88 (109—67)
81	men	2	356 (452—261)	260 (330—191)	391 (539—243)	304 (400—208)	86 (100—72)
	women	1	330	226	348	226	81
82	men	1	295	191	295	226	93
	women	2	373 (452—295)	251 (295—208)	347 (382—313)	217 (226—208)	87 (103—72)
83	men	1	330	243	382	278	93
	women	2	356 (365—348)	252 (261—243)	391 (418—365)	261 (261—261)	100 (105—96)
84	men	2	304 (330—278)	217 (243—191)	312 (330—295)	217 (243—191)	102 (104-100)
	women	1	313	208	330	226	89
87	men	1	295	191	278	226	110
	women	1	261	113	226	156	121**

The diameters, long and short, of large follicles, and the frequencies/mm² of follicles in small follicle areas indicate the averaged values. Figures in parentheses: Range.

* Sex difference of the follicle size is relatively marked.

** Sex difference of the follicle size is marked (Follicles of men are greater).

tained up to the end of the sixties. Thereafter, the difference disappeared and an inverse relation was rather found.

d) Budding Process and Sanderson-Damberg's Bolster-Like Swellings of Follicle Walls

The association of follicles was the only accurate direct evidence of proliferation of the follicles through solid budding processes (Fig. 30). Hollow budding process was often in the large follicles. The hollow buds appeared as one or a few small satellite follicles just around the parent follicles in consecutive sections and became independent follicles losing communication with the cavity of the parent follicle.

The Sanderson-Damberg's bolster-like swellings of the follicle wall were found in large to medium-sized follicles and consisted of single columnar follicle epithelium with long oval, darkly stained nuclei, a number of small follicles and engorged capillaries included herein (Fig. 31). The swellings were often similar in appearance to the infoldings of the acinar follicles, but different from the infoldings in the following two points — the columnar follicle epithelium and engorged capillaries. No mitotic division of the follicle wall occurred. The production of new follicles through solid budding processes of the follicle wall was not found but rarely hollow buddings were seen. Some of these swellings contained no small follicles and consisted of merely the columnar follicle epithelium and engorged capillaries. They may be considered to be the relatives or precursor swellings.

The Sanderson-Damberg's bolster-like swellings and their relatives began to appear from late childhood (6 years old) and increased in frequency from early adult life to the presenium (Table 5). The relation between the occurrence of these swellings and the follicular types observed was not always definite. In early and late adult life, they occurred in the glands which appeared macrofollicular — averaging 75 to 50 frequencies per mm^2 of follicles in small follicle areas. In the

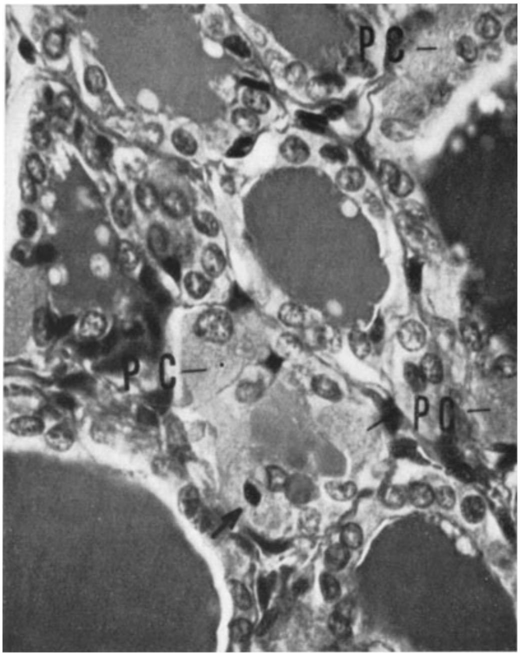

Fig. 21. Two months old female baby. Parafollicular cells (PC) are scattered just around the follicles and do not limit the follicle cavity directly. They are far larger than the follicle cells and have a larger nucleus which contains a loose chromatin reticulum and a prominent nucleolus. Some show no nuclei. With cells of great size it can be expected that many sections occur in which nuclei are not visible. A few are in a stage of degeneration. Ciaccio. Hematoxylin and eosin. × 560

presenium and senium, they occurred not only in the glands of macrofollicular-microfollicular mixed type but also in those of microfollicular type. A relation between their occurrence and sex difference appeared to exist. In men the swellings increased in the presenium while in women they increased earlier — in early adult life (Table 5).

2. Follicle Cells

Follicle cells were low cubical, approximately 7 μ high and 9 μ wide, sometimes squamous, 3 μ high and 10 μ wide, or columnar, 9 μ high and 7 μ wide. Generally, from immediately after birth to 10 months, they were high cubical throughout the entire area of the gland (Fig. 21). Further from early childhood to puberty, they remained high cubical (Fig. 23).

From approximately 17 years on, they became variable in height. Between 25 and 44 years, they were chiefly low cubical not only in small follicles but also in medium-sized and large follicles (Fig. 24), and showed no significant relation in height with the follicle (size, shape and location) and colloid (staining, homogeneity and vacuolation) conditions. Thereafter, the follicle cells showed never further decrease in height but became often rather high cubical in the presenium and senium (Fig. 22).

The nuclei were round to oval but flattened in low cubical follicle cells and elongated in high columnar follicle cells. The long diameters averaged 7 μ, ranging from 9 to 4 μ and the short diameters 5 μ, ranging from 7 to 3 μ. The chromatin reticulum was moderately dense and contained a round small eosinophilic

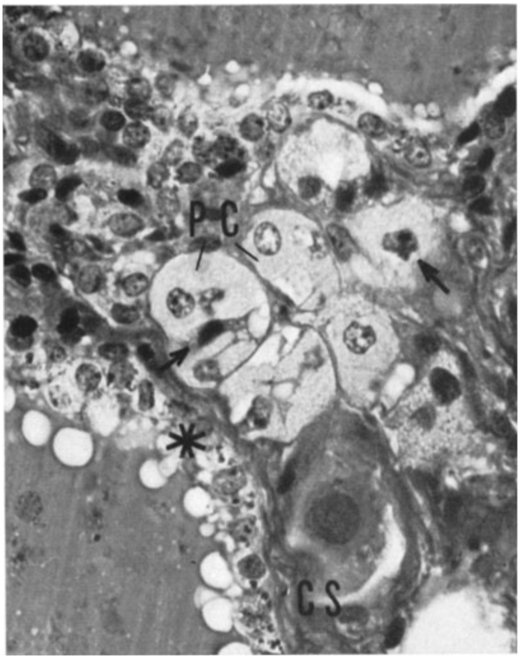

Fig. 22. 55 years old woman. Parafollicular cells found in groups. Some are arranged like a small vesicle. Their nuclei are partly pyknotic (arrows). Ordinary follicle cells contain yellowish brown pigment granules (asterisk) while parafollicular cells do not contain them. Just near the parafollicular cells a follicle-like small cyst (CS) is seen. Its epithelium is single, low cubical and has irregular-shaped pyknotic nuclei. The epithelium contains no yellowish brown pigment granules. The content of the cyst looks like the colloid but somewhat inhomogeneous, and contains a desquamated cell. Ciaccio. Hematoxylin and eosin. × 560

nucleolus. The cell boundaries were more or less distinct with relatively prominent eosinophilic terminal bars in the apical margins. The cytoplasm was feebly eosinophilic and granular, and contained sometimes one or a few eosinophilic colloid droplets in the apical zone. Yellowish brown pigment granules were also found here and further lateral to the nuclei. Their distribution was not uniform but variable from follicle to follicle, and even in one and the same follicle. They appeared for the first time in the 6 years and always found from 12 years old on. In the presenium and senium they were abundant (Fig. 22).

Some of the follicle cells had giant nuclei which ranged from 11 to 9 μ in the long diameter and from 9 to 7 μ in the short diameter. The chromatin reticulum was sometimes moderately dense with or without a prominent nucleolus and sometimes faint and coarse always with a more prominent nucleolus. These follicle cells with giant nuclei were also larger in size than ordinary follicle cells and ranged from 15 to 9 μ in height and 15 to 9 μ in width. The cytoplasm was very faint and its granularity was invisible. They were scattered in small numbers throughout the entire gland and were found often in late adult life, further in the presenium and senium. They showed no special relation with the follicle and colloid conditions.

Degeneration of the follicle cells appeared to be rare, with a few to several desquamated cells with a pyknotic or faintly stained nucleus, which were swollen or shrunken in the colloid (Fig. 33) and to increase in degree in the presenium

Table 7. *Structures of ultimobranchial origin found in the human thyroid gland*

Age	Sex	Lobe related	Extent			Cysts and vesicles contained		
			long diameter μ	short diameter μ	cranio-caudal diameter μ	No.	long diameter μ	short diameter μ
2 years 8 months	woman	right	174	104	180	1	59	35
12 years	man	right	261	261	240	—		
21 years	man	left	696	609	1200	3	175— 70	175— 70
23 years	man	right	1252	522	520	4	528— 34	422— 34
26 years	man	right	870	522	1680	23	435—174	261— 87
33 years	man	left	609	522	340	6	157— 87	122— 52
52 years	man	left	522	261	700	5	340—226	226—174
61 years	man	left	365	174	120	—		
68 years	man	right	991	435	—			
72 years	woman	right	522	174	580	2	87— 69	69— 52
74 years	man	left a	261	226	280	1	218	200
		b	522	348	460	2	433— 70	121—105
75 years	man	right a	174	87	60	—		
		b	433	348	420	2	35— 17	21— 10
84 years	man	right a	348	261	620	1	59	42
		b	295	121	500	—		

a and b are located far away from each other.

and senium. Involution of the follicles appeared to go on slowly or rapidly by continued desquamation of a few or several follicle cells. Mitotic figures of the follicle cells were not found throughout postnatal life.

3. Parafollicular Cells

Parafollicular cells were rarely found and were identical in appearance with those already reported in rodents and dogs by the present author and his colleagues (SUGIYAMA, 1939, in rats; 1942, in mice; 1950, in rabbits; 1954, in guinea pigs; SATO, 1959, in hamsters; TASHIRO, 1964, in dogs). They were seen in the central zone of the lobes of two thyroid glands taken from a two months old female infant and a 55 years old woman (Figs. 21 and 22). The parafollicular cells remained without bordering the follicle cavity directly. They appeared as single elements or in groups forming an epithelial plate on the follicle walls directly. The nuclei were round to oval, slightly eosinophilic and larger than those of the follicle cells, 10 to 7 μ in the long diameter and 9 to 5 μ in the short diameter, but were smaller in size than the giant nuclei of the follicle cells. The chromatin reticulum was always loose, somewhat eosinophilic and very fine, containing a round eosinophilic nucleolus. The cell body was oval and sometimes polygonal when in groups, far larger than the ordinary follicle cells — 27 to 14 μ in the long diameter and 19 to 10 μ in the short diameter, and was eosinophilic granular. A few of the parafollicular cells were degenerating with pyknotic nuclei and strongly eosinophilic coarse granules in the cytoplasm. No intermediate forms between the parafollicular cells and the follicle cells were found. Just near a group of the parafollicular cells, a follicle-like small cyst was found and contained colloid-like but slightly inhomogeneous material and a desquamated cells. The

Table 8. *Frequencies of occurrence of tubular follicles which appeared among follicles over 100 μ in craniocaudal diameter in follicle groups selected at random in different zones of the lobe*

Age & Zones	No. of follicles examined	Ordinary follicles 100—200 μ	over 200 μ	Tubular follicles 100—200 μ	over 200 μ
10 hours after birth * intermediate zone	16	14	2	—	—
9 months old					
peripheral zone	15	14	1	—	—
central zone	5	5	—	—	—
One year and a half					
peripheral zone	35	30	4	1	—
central zone	30	26	2	2	—
Two years old					
peripheral zone	30	25	2	—	3
central zone	19	17	2	—	—
Three years old					
peripheral zone	54	46	7	1	—
central zone	40	39	—	1	—
6 years old					
peripheral zone	55	40	14	—	1
central zone	77	69	6	1	1
17 years old					
peripheral zone	19	12	4	1	2
central zone	27	24	—	—	3

* Premature birth (corresponding to 32 weeks of prenatal life).

epithelial cells of the cyst was low cubical and more eosinophilic and had irregular-shaped nuclei. The epithelial cells were different in appearance from ordinary follicle cells, not containing any yellowish brown pigment granules (Fig. 22), but rather were the epithelial cells of the cysts of ultimobranchial origin.

Solid cell masses and cords found between follicles were demonstrated to be tangential sections of follicles by observing serial consecutive sections and accurately confirmed by making folliculograms. They were embodied into the follicles.

4. Ultimobranchial Tissue

In the central zone of the lobe or in the posterolateral or posteromedial part of the peripheral zone, there occurred sometimes enigmatic structures consisting of a few to several solid cell cords and cell conglomerates and cysts (Figs. 23 to 26 and Table 7). They were of ultimobranchial origin and showed no significant change with age. These structures were found in the right or left lobes of 2 years 8 months old, 12, 21, 23, 26, 33, 52, 61, 68, 72, 74, 75 and 84 years old cadavers. No significant difference in occurrence and size between man and woman was found. Parafollicular cells were not found near these structures. The structures were more or less branched and their extent varied from case to case. Rarely, two same structures were located far away from each other (Table 7). They were also directly or closely in contact with the follicles and some of them enclosed completely the follicles. Lymphocytes were scattered in the surrounding connective tissue.

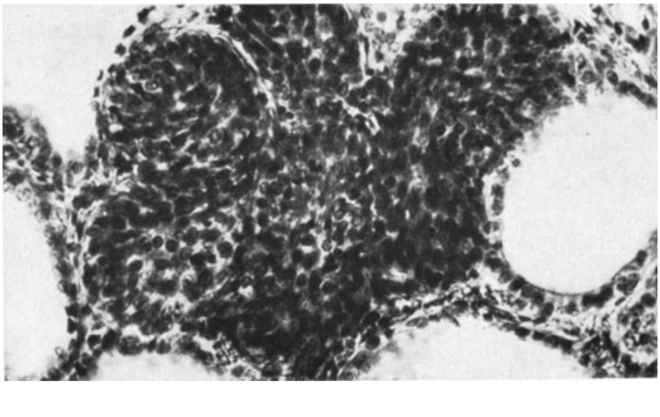

Fig. 23

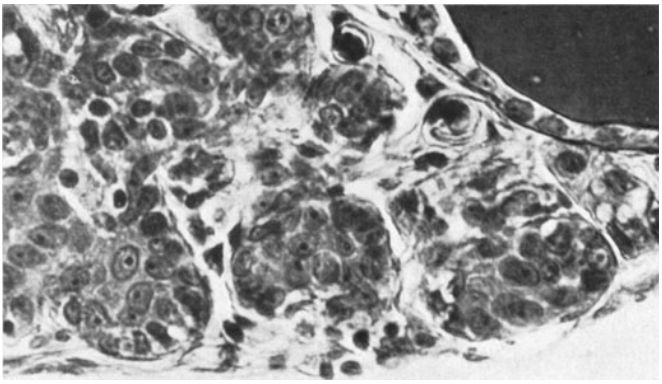

Fig. 24

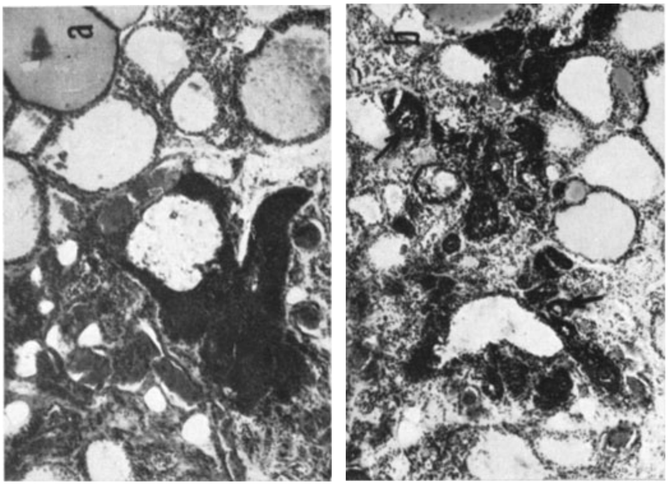

Fig. 25 a and b

Fig. 23. 12 years old male child. Ultimobranchial cell cords and conglomerates are seen between the follicles. The nuclei are closely packed and the cytoplasm is scanty. The cell boundaries are not distinct. Formol. Hematoxylin and eosin. × 280

Fig. 24. 33 years old man. Ultimobranchial cell cords are seen. The nuclei are of different sizes and sometimes contain a prominent nucleolus. Ciaccio. Hematoxylin and eosin. × 560

Fig. 25a and b. 52 years old man. Ultimobranchial cell cords, cell conglomerates and cysts are seen. One of the cysts contains many eosinophilic cell debris. In the cell cords and conglomerates small cavities (arrows) are produced by degeneration of the epithelial cells. Formol. Hematoxylin and eosin. × 55

In the cords and conglomerates epithelial cells were closely packed but partly loosely arranged. The nuclei were round to oval and almost as large as those of the follicle cells, and contained a moderately dense chromatin reticulum. Some of them were slightly enlarged and contained a loose chromatin reticulum. The cytoplasma was scanty and slightly basophilic or strongly eosinophilic. Yellowish brown pigment granules were not found. The cell boundaries were indistinct. In the central parts of cell cords and cell conglomerates, a small number of pyknotic and metachromatic nuclei were found. Near them, feebly eosinophilic, vacuolated and granular materials were found. This involved initiation of cysts or vesicles formation. A few to several cysts were found in or near the cell cords and cell conglomerates and were different in diameter (Table 7, Fig. 25). Some of them were indistinguishable from the follicles. The cavities contained a homogeneous and/or inhomogeneous, coagulated eosinophilic material, sometimes together with a few desquamated cells. The wall of the cysts consisted of a single low cubical to stratified but not ciliated epithelia. The epithelial cells of the cysts contained no yellowish brown pigment granules and some of them were eosinophilic and had irregular-shaped nuclei. In a 26 years old cadaver, the structure appeared as a part of the parathyro(IV)-thymo(IV)-ultimobranchial complex (Fig. 26). The histological structure was the same as that found in other structures.

5. Follicle-Like Structures

There appeared sometimes other follicle-like structures of unknown origin and nature, and were sparsely distributed in a random fashion in the central zone of the lobe (Fig. 32). The structures were generally round to oval, sometimes irregular-shaped, and rarely developed to complicated branching alveolar structures. Around the structures, a very slight lymphocyte infiltration was also found. The structures were limited by a single columnar epithelium. The epithelial cells were not ciliated. The nuclei were oval and contained a dense chromatin reticulum. The nucleoli were not prominent, but sometimes one or two large eosinophilic spherules were contained in the nuclei. Furthermore, yellowish brown pigment granules were contained in the apical zone and as many as or sometimes more than in the follicle cells. The cavities contained granular, sometimes vacuolar, feebly eosinophilic or basophilic material together with several desquamated cells and rarely wandering cells.

6. Colloid

Colloid ranged in staining from feebly to moderately eosinophilic, and was homogeneous, and showed a little marginal vacuolation frequently with a central or an eccentrical large vacuole. The large vacuole contained sometimes a small amount of basophilic granules. The colloid contained in large to medium-sized follicles situated in the peripheral and central zones of the lobe and in the isthmus was not intensely stained but rather moderately or variably stained. The colloid contained in small and very small follicles was poorly stained. Desquamation of the follicle cells into the colloid appeared to be dependent upon the length of time elapsing between death and fixation after autopsy. The desquamation of a few to several follicle cells considered to be a vital phenomenon was found partly together with a few wandering cells in the cavity (Fig. 33) and sometimes seen in the presenium and senium.

Immediately after birth the colloid was uniformly contained in all of the follicles (Fig. 6). It was feebly eosinophilic, dilute and homogeneous, but showed no increased vacuolation. Further, no significant desquamation of the follicle cells was found in the colloid. Thereafter, the colloid increased in amount with the change of the gland to macrofollicular type (Figs. 7 to 12) and was most abundant from the late stage of early adult life to the beginning stage of late adult life

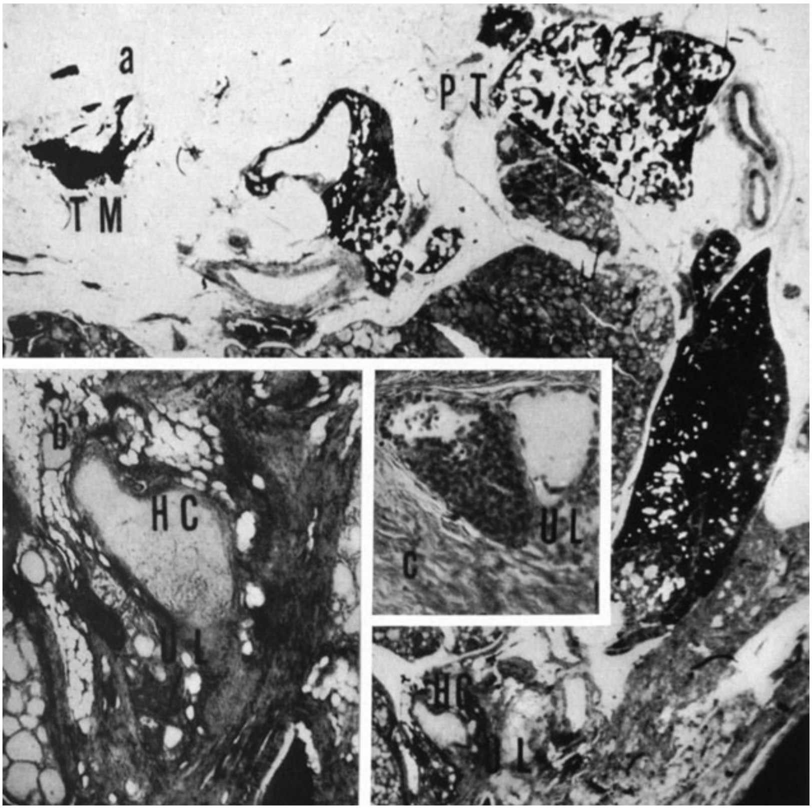

Fig. 26a—c. 26 years old man. The ultimobranchial cell cords and cyst appear as a residual part of the parathyro(IV)-thymo(IV)-ultimobranchial complex (parathyroid part: PT; thymic part: TM). The ultimobranchial part (UL) is separated from the parathyroid part by a piece of ectopic hyaline cartilage (HC). Formol. Hematoxylin and eosin. a — × 15; b — × 30; c — × 40

(Figs. 13 and 14). During this period the colloid contained in large and medium-sized follicles was moderately eosinophilic and homogeneous. After this period, the colloid decreased in amount gradually with variable staining intensity and concentration (Figs. 15 to 17). In the senium the colloid was not constant in staining — gradually feeble in staining and diluted but sometimes intense (Figs. 18 to 20).

The colloid indicated sometimes slightly increased vacuolation in a part just close to the Sanderson-Damberg's bolster-like swellings and their relatives, but not always decreased in staining intensity here.

7. Blood Vessels, Arterial Buds, and Funnel-Shaped Sphincter Apparatuses

The blood vessels were abundant in the human thyroid gland. The branches of the superior and inferior thyroid arteries found in the capsule ran into the interior of the gland, within the primary and secondary connective tissue septums, together with the tributaries of the veins. The arteries had well-developed three layers together with a prominent lamina elastica interna in adults. The veins were less developed, especially in the media, and some of them possessed the intima

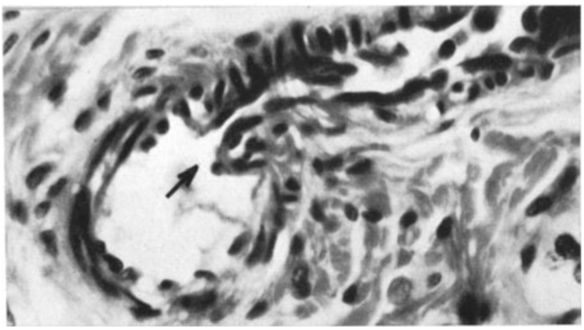

Fig. 27

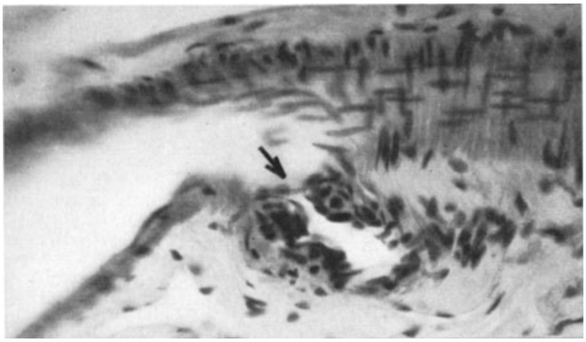

Fig. 28

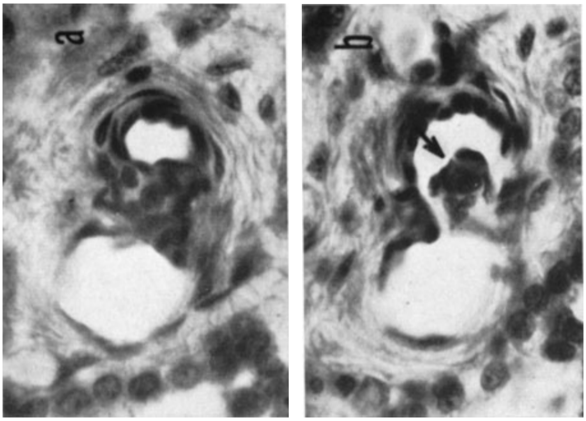

Fig. 29 a and b

Fig. 27. One year and two months old male child. A funnel-shaped sphincter apparatus appears as two lip-like valvules (arrow) at the branching point of the artery. The main component is smooth muscle fibers circularly arranged. Formol. Hematoxylin and eosin. × 560

Fig. 28. 53 years old man. Three arterial buds (arrow) appear near the branching point and project into the cavity of the artery branch. The main component is also smooth muscle cells. Formol. Hematoxylin and eosin. × 280

Fig. 29a and b. 42 years old man. An arterial bud (arrow) appears at an arteriovenous anastomosis and projects into the cavity of the artery. Formol. Hematoxylin and eosin. × 560

and adventitia only. Capillaries, ordinary and partly sinusoidal, were abundantly seen around the follicles and were surrounded circularly with argyrophilic fibers which at the same time enclosed just directly the follicles. No characteristic histological changes of the arteries and veins were found with increase of age.

Arterial buds consisted of endothelium and a few muscle cells derived from those of the media but had no elastic fibers. They appeared as half-spherules or as small papillae projecting towards the cavity of the artery. Most of them appeared singly or in groups of a few, sometimes 6, not only at the branching point itself but also in the neighboring parts of the parent artery and its branch (Fig. 28). Some were found in the non-branching ordinary parts included in straight, bending and winding courses of the artery and further rarely in the arteriovenous anastomoses (Fig. 29). The arterial buds were usually 12 to 21 μ wide at the bases (maximum: 70 μ and minimum: 7 μ) and 12 to 18 μ high (maximum: 46 μ and minimum: 7 μ). The cross sections of the arterial buds were oval, being 14 to 21 μ in the long diameter and 12 to 14 μ in the short diameter. The long diameter ran parallel with the course of the artery. The arterial

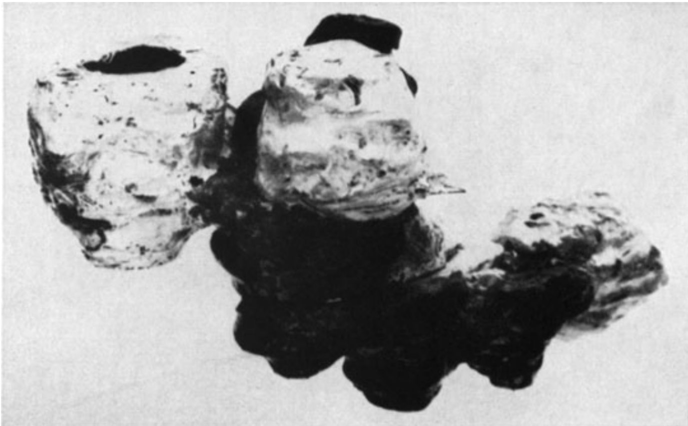

Fig. 30. Wax plate reconstruction model. Follicles associate with each other by connection of their epithelial walls, without communication of their cavities. 7 days old male newborn baby. × 500

buds appeared for the first time shortly after birth and thereafter increased in frequency, being most frequent between 30 to 60 years old.

The arteries and their branches were of different calibers in the neighborhood of the branching points connected with these arterial buds. The parent arteries were usually 30 to 60 μ in diameter, rarely 200 μ or 400 μ, and the branches 20 to 50 μ. The ordinary parts concerned with the arterial buds of the arteries were 30 to 70 μ. All of these were found not only in the capsule, but also in the peripheral and central zones of the lobe and in the isthmus. Especially, they were most frequently seen in the posterior half of the peripheral zone of the lobe and subsequently in the posterior half of the central zone, and relatively often in the isthmus.

Funnel-shaped sphincter apparatuses were found at the branching point of the arteries (Fig. 27). The apex projected towards the cavity of the parent artery, and the base was situated at the branching point. In longitudinal section, they appeared as two lip-like valvules and in tangential section as half-spherules. The main components were a few circularly arranged smooth muscle fibers and endothelial cells. They appeared relatively often in early life but rather rarely in late life. This was in contrast in time relation with the finding of the arterial buds. The sphincter apparatuses were approximately 17 μ high and 24 μ wide at the base. The parent arteries were about 42 μ in diameter in the neighborhood of the branching point and the branches about 24 μ. A similar situation existed not only in the heights and widths of these two structures, but also in the diameters of the parent arteries and their branches.

Perifollicular capillaries were abundant and circularly surrounded by argyrophilic fibers which enclosed the follicles directly. They were often engorged and appeared to be intraepithelial (BUCHER, 1940) in early life, especially during the newborn and suckling periods. From late childhood to the beginning stage of late adult life, they maintained almost the same condition. Thereafter, they began to decrease in number and this was marked in the senium, especially in the peripheral zone of the lobe.

8. Connective Tissue

The capsule was connected with the fascia cervicalis, perimysium of the infrahyal muscles, sheaths of the common carotid artery and internal jugular vein, and adventitias of the esophagus, larynx and trachea.

The capsule was divisible into two layers, internal and external, in the major part, especially in its medial and posterior parts, but was single in the minor part, transforming immediately to the perimysium and adventitias of the trachea and esophagus (Figs. 6 to 20). The internal layer was composed of dense connective tissue which contained relatively abundant elastic fibers but no argyrophilic fibers, and the external layer of loose connective tissue which containt more or less abundant fat tissue but no argyrophilic fibers. From the newborn and suckling periods to early childhood, steatoblast tissues were seen here. Rarely, small lymphocyte infiltrations were seen around the blood vessels. They did not develop to form lymphatic nodules.

The capsule varied in width topographically from approximately 1800 to 180 μ in adults and was wide along the posterolateral and posteromedial parts of the lobe which were near the larynx, trachea and esophagus. The width depended upon age but was variable from material to material even in the same age. It depended upon the way of removing the gland from the neighboring organs.

The septums were divided into two kinds, primary and secondary. The primary septums came from the capsule directly and contained relatively large blood vessels and sometimes nervous bundles. They contained abundant elastic fibers and sometimes several fat cells, but no argyrophilic fibers. They were about 522 to 348 μ in width. The secondary septums varied in width and appearance from material to material even in the same age. They were abundant only along the course of the blood vessels and usually discontinuous in amount. The parenchyma limited by the secondary septums was variable in follicle appearance. The thyromeres also were not always limited by the secondary septums. The secondary septums were 52 to 87 μ in width and relatively abundant in the newborn and suckling periods and in childhood. They contained relatively abundant elastic fibers but no argyrophilic fibers. They contained very rarely a piece of hyaline cartilage (Fig. 26). Small lymphocyte infiltrations were found rarely around small blood vessels contained here but did not develop to lymphatic nodules.

Perifollicular connective tissue was 2 to 7 μ in width, but varied depending upon the engorgement of perifollicular capillaries. It consisted of dense networks of argyrophilic fibers throughout life which became thick in the presenium and

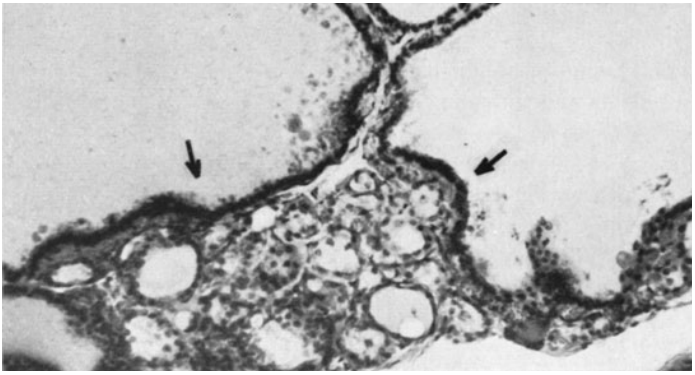

Fig. 31

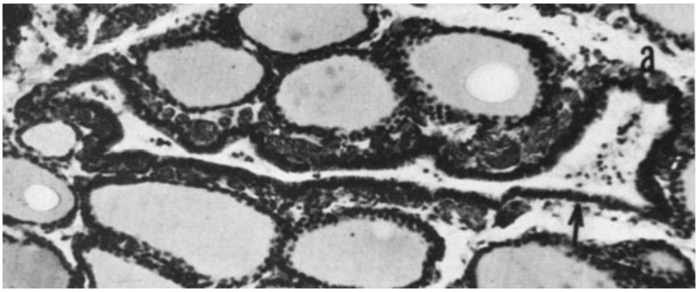

Fig. 32a

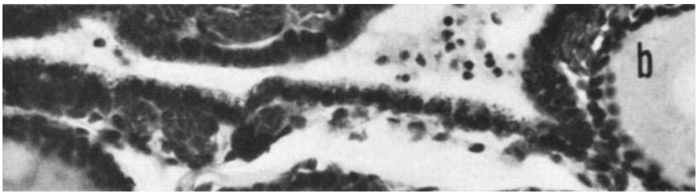

Fig. 32b

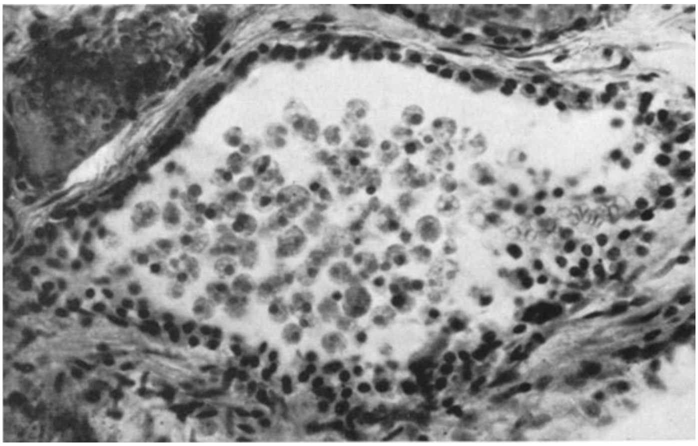

Fig. 33

Fig. 31. 47 years old man. Sanderson-Damberg's bolster-like swellings (arrows) are seen. They consist of columnar follicle epithelium with closely arranged, chromatin-rich nuclei, engorged capillaries and a number of small follicles. Formol. Hematoxylin and eosin. × 140

Fig. 32a and b. 30 years old man. An irregular-shaped structure (arrow) of non-ultimobranchial origin is seen. The cavity contains a number of desquamated cells. Epithelial cells are columnar and have darkly stained, chromatin-rich nuclei. Yellowish brown pigment granules are abundant in the apical zone of the cells. Formol. Hematoxylin and eosin. a —× 140; b — × 280

Fig. 33. 43 years old man. A follicle is in degeneration and contains many roundly swollen, desquamated follicle cells with faintly stained nuclei in feebly stained colloid. Formol. Hematoxylin and eosin. × 280

senium, especially near the septums and capsule. It contained further a few elastic fibers, for the first time in 7 years old children and usually in the senium. The elastic fibers were merely continuations of those contained in the adventitia of the blood vessels and usually did not form networks. They were slightly abundant near the septums and capsule. They were also variable in amount from material to material even in the same age.

Colloid-like eosinophilic materials were seen in the septums and perifollicular connective tissue, also in some of the veins. These pictures appeared to depend upon the length of time elapsing between death and fixation. The material found in the veins appeared to be coagulated blood plasma and the material in the interstitium to be the colloid which outflowed through the loosened follicle walls, or to be tissue fluid.

Small pieces of thymic tissue were found rarely in the posterior part of the peripheral zone and in the posterior half of the central zone of the lobe. They contained Hassal's bodies. The thymic tissue showed an involution replaced by fat tissue (Fig. 26). In a 26 years old cadaver the thymic tissue appeared as a part of the parathyro(IV)-thymo(IV)-ultimobranchial complex in the posterior part of the peripheral zone of the lobe (Fig. 26).

Discussion

ORATOR and SCHLEUSSING (1931) observed the postnatal development of the human thyroid gland and noted the following: In the newborn the thyroid glands are solid. The histological development is found to start in the regions of the polar and peripheral zones of the lobe and prevails over the central zone by forming central vesicles (Zentralbläschen) of the lobules in which the colloid has not yet appeared. These central vesicles soon become central colloid vesicles (Zentralkolloidbläschen) to acquire the colloid. This development begins in the second month and persists through the 6th month to the second year. Around the second year the colloid appears also in the solid parenchyma surrounding the central colloid vesicles, and shortly after the diffuse colloid thyroid gland — young colloid type (diffuse Kolloidschilddrüse, Jungkolloidtyp) develops. This type persists from the third to 10 years. Beyond 30 years, the thyroid gland does not proliferate but rather shows decrease in follicle size and colloid content. An earlier observation of the thyroid gland shortly after birth to 29 years old (ORATOR and WALCHSHOFER, 1927) described a similar developmental pattern: The newborn thyroid gland is solid and the lobule consists exclusively of colloid-free parenchyma surrounding a central slit cavity. The thyroid gland grows, through two stages of central vesicle type (Zentralbläschentyp) and children type (Kindertypus) between two and 9 years, to the adolescent thyroid gland (Jugendschilddrüse) at puberty and the mature thyroid gland (Reife-Schilddrüse) later. The central vesicle type contains a developing but colloid-free central vesicle surrounded with solid parenchyma in the lobule and the children type a developed central vesicle which acquired the colloid but was surrounded with solid parenchyma. The adolescent thyroid gland consists of all colloid-containing follicles of different sizes, while the mature thyroid gland contains uniformly large colloid-containing follicles. The two observations are somewhat different in developmental pattern from the present data and in sharp contrast in that the human thyroid gland immediately after birth is seen to consist of all well developing colloid-containing follicles (Fig. 6). KRINSKAJA (1932) and KOCH (1938) reported the same findings in the newborn thyroid gland.

The observations on the life curve of the histological pictures in the normal thyroid gland of the Japanese people (DE OCA, 1930) indicated the possibility of two peaks of follicle growth, that the gland is parenchymatous-microfollicular until puberty, macrofollicular in puberty and thereafter to 35 years, microfollicular up to 45 years, of mixed type of small and large follicles up to 60 years and later again microfollicular. Another observation (BÜCHNER, 1924) showed in a similar manner that diffuse dilation of follicles occurs at puberty, transitional type between macrofollicular and microfollicular types appears between 20 and 30 years, and microfollicular type between 40 and 50 years and macrofollicular type beyond 60 years.

Different peaks of follicle growth have also been reported in still other studies. MAY (1928) described that the first peak, higher and earlier in women than in men, occurs at puberty and the second peak takes place only in men after 60 years. According to SAKA (1935), the human thyroid gland is of microfollicular type in childhood and before puberty, fairly microfollicular-macrofollicular and macrofollicular in type between 17 to 25 years, macrofollicular from 26 to 35 years, and finally again microfollicular and parenchymatous from 50 years on, although the gland shows the second peak of follicle growth between 60 and 65 years. TAKAYA wrote also of two peaks, the first in the twenties and the second in the fifties. On the other hand, several functional critical terms of the human thyroid gland have been described. VOGELER (1929) studied the feeding effect of human thyroid material upon tadpoles and found that three peaks of the effect occur at birth, at puberty and in the senium commonly in men and women, but another peak in the postclimacterium.

The present data based upon the quantitative measurements of follicles showed that the human thyroid gland changes successively in follicular pattern — from microfollicular type, passing through three stages of microfollicular-macrofollicular, macrofollicular and transitive macrofollicular types to macrofollicular-microfollicular type and finally return to microfollicular but regressive type (Figs. 1 and 6 to 20). This finding differs from those of the above writers. In the senium the gland becomes microfollicular and does not appear to produce the second peak of follicle growth. DOGLIOTTI et al. (1935) and ASCHOFF (1938) also indicated the diminution in follicle size in the senium. The macrofollicular type appears around the twenties (from the late stage of early adult life to the beginning stage of late adult life) and this corresponds to a peak of follicle growth. At puberty the human thyroid gland shows no characteristic change in follicular pattern but rather a transitional form to the adult form (Figs. 10 to 12). According to STEFKO (1934), the follicles grow slowly between 5 to 7 years and rapidly between 8 to 10 and 11 years to reach the maximum at 15 to 16 years. SELZER (1936) reported that the gland shows no special mark at puberty and is identical with the normal glands of adults.

The data concerning the size of the follicles of the adult thyroid gland have been different, probably due to different ways of measurement. MÜLLER (1896) observed that relatively large follicles are 200 to 250 μ and small follicles 30 to 66 μ. Further, in other studies, the follicles have been generally described to be from 20 to 300 μ, sometimes to 500 μ, exceptionally to 1 mm (DE QUARVAIN, 1904); from 20 to 300 μ (SARBACH, 1906); from $^1/_4$ to $^1/_2$ mm, some from $^3/_4$ to 1 mm (SANDERSON-DAMBERG, 1911); with the upper limits of 320 μ in a 28 years old man (SOBOTTA, 1915); from 35 to 500 μ (WEGELIN, 1926); average 300 μ with a range of 150 to 500 μ (WILSON, 1927/28); 0.02 to 0.897 mm (RIENHOFF, 1929); 45 to 250 μ, sometimes to 500 μ or more (KOHN, 1930); 163.24 μ in average (JACKSON, 1931); 47 to 413 μ between 20 to 35 years (SAKA, 1935); 9—309 μ in maximum length (STEIN, 1937); 50 to 400 μ (RICE, 1938) and from 35 to 250 μ, sometimes to 400 to 500 μ (BONFIGLI et al., 1960).

The follicles vary in diameter also depending upon age. VERSON (1872) wrote that the follicles are 100 to 160 μ already in newborns and over 200 μ in adults. HESSELBERG (1910) observed that the follicles range from 30 to 300 μ in the first 6 months. KOCH (1938) reported the follicles of newborns to be 45 to 70μ in size. According to ISENSCHMID (1910), the largest follicles are often slightly over 100 μ in the one year old, often 200 μ in the 5 and 6 year olds, sometimes over 200 μ in the 7 and 8 year olds, and most follicles to be over 250 μ in the 12 and 15 year olds. BENAZZI (1926) described that the follicles range from 30 to 160 μ in children and 60 to 220 μ in adults. CLERC (1912) reported in the senile thyroid gland of over 50 year old that the follicles average 75 to 90 μ, sometimes showing large values of 80 to 150 μ. Serial data of detailed quantitative measurements have been differently reported. HELLWIG (1920) described that the follicles are on the average below 50 μ during the first half year, 80 μ from over one half year to 4 years, 160 μ from 16 to 25 years, 150 μ from 26 to 50 years and 50 μ in over 50 years. SCHAER (1928) wrote that the follicles grow rapidly to 150 μ at 5 years, 350 μ around 20 years, reaching the maximum values (400 μ) at 25 years, and thereafter decrease with values of 100 μ from 60 years on. RICE (1931) reported that the follicles average 60 to 70 μ at birth. Immediately after birth they decrease to 50 μ in diameter and return again to the original values at the end of 6 months. From 6 months until puberty the follicles rapidly increase in size reaching the maximum of 240 to 250 μ between 13 and 15 years in men and between 17 and 20 years in women. They decrease gradually through the productive period of life dropping to 180 to 200 μ at 60 years and remain stationary throughout the rest of life. THOMAS (1934) described that the majority of follicles are 200 μ in size and a few attain maximum values of 550 to 700 μ at 9 years, over 400 μ at 21 years and over 500 μ, some reaching 700 μ, at 31 years.

The present data showed in detail that the follicles vary in diameter depending not only upon age but also upon location of their distribution, and further that they vary from individual to individual even in the same age (Figs. 2 to 5). The averaged values of the large follicles range between 400 and 600 μ from the end of early adult life to the beginning of late adult life (Figs. 13 and 14), during which time the glands are exclusively macrofollicular, and thereafter decrease (Figs. 15 to 20), significantly from 40 years on. The maximum values of the large follicles are rarely over 1000 μ and are seen not only in the peripheral zone of the lobe but also in the central zone and in the isthmus. In the seventies and eighties exceptionally large follicles remain as cysts.

It is of histogenetical interest that, until the beginning of late adult life, the large follicles grow to a far greater degree in the peripheral zone of the lobe, especially in its posterior part, to a lesser degree in the central zone, particularly in its anterior half, and to the least degree in the isthmus and pyramidal lobe (Table 9), while from the middle of late adult life on this significant difference in growth begins to diminish and in the senium almost completely disappear due to accelerated regression of the peripheral large follicles (Figs. 2 to 5 and 6 to 20).

Comparison between the follicular patterns of man and woman (Table 6) gives us an impression that the follicles, especially large follicles, are slightly greater in man than in woman, but appears to be in an inverse relation from the seventies on. RICE (1931) depicted that the man and woman curves of follicle size are at first coincident but the woman curve begins to be lower than the man curve from 40 years on. OOSUGI (1960) described that the follicles are averagely larger in man.

The shapes of the follicles have been differently reported. VIRCHOW (1865) stated that the follicles contained in the lobule are not merely an aggregate of isolated vesicles but rather a system of follicles which often communicate with each other having vesicular outgrowths and projections. Recently, HAMMER and LOESCHCKE (1934) described a similar finding — the extension of the follicle cavities to the collecting duct system (an arboreal system, Drüsenbäumchen, of the follicle cavities). STREIFF (1897) and MAZIARSKI (1902) found that besides round to oval follicles there occur tubular or irregular-shaped follicles having semispherical pockets in the gland but no complicated communication to form a system of canals takes place. v. EBNER (1902) expressed an intermediate view — the minority of follicles to have branching cavities but the majority to be regularly round. BARGMANN (1964) described in a similar manner that the lobules often consist of only round to oval follicles while some contain collecting-duct-like central canals, around which follicles are grouped, a number of them communicating with the canals.

Folliculograms indicated that branching irregular-shaped acinar follicles are more numerous than hitherto assumed in the normal human thyroid gland (Table 4). A considerable number of medium-sized follicles between 100 and 200 μ and larger follicles of over 200 μ are found to be irregular-shaped forming a few alveolar pockets and rarely 5 pockets. They may correspond to the acini of KUHLENKAMPFF (1950). The formation of the acinar follicles is generally increased in proportion to the increase in age and follicle size. On the other hand, SATTLER (1930) suggested by observing Basedow's disease that highly irregular-shaped follicles are produced by two factors — 1. the follicle walls relaxing due to diluting colloid and 2. epithelial proliferation. Earlier, WILSON (1927/28) also indicated a similar picture of a pathological configuration by making wax plate reconstruction models. Too much branching and too many distribution of irregular-shaped follicles may be supposed to be produced due to some pathological causes.

Tubular follicles, in a literal sense, which do not produce follicle triangles, show no histological characteristics indicating them to be central canals (ZIELINSKA, 1894; KRAEMER 1910; KLOSE, 1916; ASCHOFF, 1925; LOESCHCKE, 1937), collecting ducts (HAMMER and LOESCHCKE, 1934; EWE, 1936) and columnar epithelium tubes (WEGELIN, 1926: Zylinderepithelschläuche). Tubular follicles appear to increase in frequency with age but do not take a central location within the follicle parenchyma limited by the connective tissue septums (Table 8).

The problem concerning the multiplication of the follicles has been the subject of repeated discussion. 1. The budding process — two types of solid and hollow, 2. the division (constriction) and 3. the formation of the bolster-like swellings of the follicle wall have been observed. Earlier, WÖLFLER (1880) pointed out the existence of budding and division, and MÜLLER (1896) merely the budding process. According to WEGELIN (1926), the budding process occurs more often than the division in children. SANDERSON-DAMBERG (1911) described three processes in the 15 to 25 year olds — 1. through formation and fusion of two opposite septums, 2. through constriction of the follicle wall and 3. through formation of bolster-like swellings of the follicle wall from which new follicles develop. CLERC (1912) did not find these swellings but rather rarely the budding process of large follicles in the senile glands. BARGMANN (1939) introduced the theory of possibility of the budding process in the Handbuch of v. MÖLLENDORFF. In the thyroid gland of Basedowian women treated with methylthiouracil, irregular-shaped follicles as central structures of the lobules have been reported to produce buds for new follicles by mitotic division (GERTEIS, 1952).

The present data indicated: The prevailing distribution of small developing follicles which are found associated with each other or with large follicles until about one half and one years to two years may be suggested to be one of direct evidences of multiplication in early postnatal life (Fig. 30). It is probable that the development of perifollicular connective tissue and capillaries from two years on inhibits even the brief persistence of the association of newly produced follicles with the parent follicles and presents insufficient direct evidence for the budding process in later life.

The Sanderson-Damberg's bolster-like swellings of the follicle wall have been described to correspond to the proliferative buds (Proliferationsknospe) of ASCHOFF (1925) and his colleagues (BÜRKLE DE LA CAMP, 1924 and EWE, 1936) in the Handbuch of v. MÖLLENDORFF (BARGMANN, 1939). BARGMANN (1964) suggested that the columnar follicle epithelium limiting the Sanderson-Damberg's swellings remains related to the colloid discharge. Earlier, GOORMAGHTIGH et al. (1934) explained that the swellings are the result of functional stimulation of the excretory zone which expands, and of the group of underlying acini which secrete colloid more actively. On the other hand, HAMMER and LOESCHCKE (1934) regarded them to be sections of branching parts of large cavities in the collecting duct system. The present results showed that no direct evidence of mitotic division and no follicle association is found here but the proliferation appears likely to go no by producing hollow buds. WEGELIN (1926) opined that the bolster-like swellings produce solid buds to develop small follicles.

SCHAER (1928) found only rarely these swellings in the 25 to 50 year olds and SAKA (1935) noted a similar observation in the goiter-free district as the swellings were found in each decade but of rare occurrence. CLERC (1912) did not find them in the glands from 50 years on. DE OCA (1930) found the proliferative buds only in the periods of two peaks of follicle growth in the Japanese. According to ORATOR and SCHLEUSSING (1931), the swellings are contained in the proliferative form of the gland, which occurs at a rate of 28% of all cases examined and increases to 75% from 20 to 25 years. They pointed out another type of proliferation; the follicular form (follikuläre Proliferation) which contains abundantly areas consisting of numerous developing small follicles and increases in frequency from 30 to 45 years. ROSENKRANZ (1935) pointed out the occasional proliferative activity in women in the menopause, and ASCHOFF (1938) in men of advanced age. RATNER (1931) found frequent proliferation in the thyroid glands of over 35 years.

The present results showed that the swellings and their relatives occur at a considerably high rate in the thyroid glands of Japanese people — in women they increase in frequency earlier in early adult life and in men later — in the presenium (Fig. 31 and Table 5).

In children's thyroid gland, the central canal, often branching and limited by columnar follicle epithelium with closely arranged, chromatin rich nuclei, has been reported to occur in the center of the lobule (ZIELINSKA, 1894). It seems likely that the central canal has been later differently considered from the normal and pathological viewpoints and the central canal has been sometimes modified also in its nomenclature. ORATOR and SCHLEUSSING (1931) and ORATOR and WALCHSHOFER (1927) applied the name of central canal to the normal development as the central vesicle. KLOSE (1916) called it in the children's gland the growth center which persists to produce new follicles even in adult life. BÜRKLE-DE LA CAMP (1924) interpreted them to be the residuals of the final branches of the thyroglossal duct which play a main role in forming adenomatous nodes. Earlier, KRAEMER (1910) described that the central canal brings about epithelial proliferation to induce an adenom. ASCHOFF (1925) considered it to be the germinal layer of the lobule, from which other follicles develop. Contrary to them, WEGELIN (1926) emphasized rather the distribution of the columnar epithelium tubes (Zylinderepithelschläuche) other than the central canals in the children's gland, which produce new follicles by forming buds from the tube wall and by dividing their tube cavities. STEFKO *et al.* (1933) pointed out the occurrence of follicle tubes with cell buds (Follikelgänge mit Zellknospen) characteristic of the Mongolian races.

The present results showed that the thyroid glands of the Japanese contain no central canal system throughout postnatal life (Figs. 6 to 20) but rather indicated that irregular-shaped follicle-like structures of non-ultimobranchial origin which occur rarely and without relation to the septums may correspond to the columnar epithelium tubes (WEGELIN, 1926) and be of follicular origin because of the abundant distribution of yellowish brown pigment granules in the apical zone of the consisting cells (Fig. 32). They may be supposed to be modified follicles of pathologic nature. GUTKNECHT (1885) reported that similar structures occur often in goiters, and GOLD *et al.* (1924) found that the central canals of similar structure appear as usual components of the lobules in adolescent goiters.

According to WÖLFLER (1880, 1883), two layers, cortical and medullary, are divisible in the normal human thyroid gland — the cortical layer is composed of concentrically arranged solid cell cords and conglomerates which correspond to less-developed material of the gland, while the medullary layer consists of tubes and vesicles. WEGELIN (1926) denied its usual occurrence.

The present results showed no distinction of these two layers in postnatal histological development of the human thyroid gland but rather the persistence of narrow bands and small islets consisting of very small and small follicles in the peripheral zone of the lobe, especially in its posterolateral and posteromedial parts, which remain outstanding in the presenium and senium. These bands and islets are small in amount and not enough to be called the cortical layer (Figs. 13 to 20).

The present results showed that the human thyroid gland is composed of numerous thyromeres which are similar in arrangement to the collecting duct system (HAMMER and LOESCHCKE, 1934; EWE, 1936) or to the central canal and its surrounding trabant follicles (LOESCHCKE, 1937). As shown in Tables 2 and 3, large growing follicles decrease inversely in their budding proliferative activity expressed as follicle association, while small follicles maintain for a considerable time the same activity. This can induce the thyroid gland to form thyromeres in the form of producing peripheral or terminal portions from the collecting ducts found in other developing glands. The present author would like to emphasize that the thyromeres may correspond to the lobules in a histogenetical sense.

The regular fashion of distribution of the thyromeres may present some problem on the main direction of histological differentiation of the human thyroid gland which appears to go on upwards and backwards. The regions which show earliest and earlier primordial development remain rather in a less-developed condition. The pyramidal lobe, isthmus and the connecting anterior half of the lobe remain composed of smaller follicles and smaller thyromeres, while the posterior half of the lobe is in a better-developed condition. It is probable that the histological development increases in degree through the thyroglossal duct, isthmus and the anterior half of the lobe towards the posterior half of the lobe, especially towards its peripheral zone and maintains this situation until the beginning stage of late adult life (Table 9 and Figs. 6 to 14). Furthermore, it seems likely that the histological regression of the gland is exaggerated in the above final zone from the middle stage of late adult life on. This is demonstrated by the marked diminution in size and scale of the thyromeres and their consisting large follicles found here (Table 9, Figs, 2 to 5 and Figs. 15 to 20).

The human thyroid gland shortly before and after birth has been reported to show serious changes. ELKES (1903) stated that the follicles disappear at birth with a chemical change in metabolism. HESSELBERG (1910) observed the same change at birth but interpreted it to be due to compression during passage through the birth canal. GLEIM (1912) wrote that the desquamation in the children's glands is physiological and decreases with age. STÄMMLER (1915) interpreted this change to be due to the thyroid gland around birth having to pass through a stage of elevated activity to enter a quiescent state soon later. WATZKA (1934) explained this phenomenon to be physiological occurring from exposure to cold after birth. ALLARA (1951a and b) found that the newborn thyroid gland is deprived of a follicular structure by sudden demands of the period immediately after birth and indicates secretion of colloid into the lymph vessels. SCLARE (1956) described that the sudden loss of colloid and the collapse of the follicles take place as main manifestations of hyperactivity in the newborn gland. Recently, EICKHOFF (1958) stated that the colloid loss with desquamation of the follicle

Table 9. *Comparison of the diameters of large follicles found in different zones (lobe, isthmus and pyramidal lobe) of the human thyroid gland*

		Lobe				Isthmus		Pyramidal lobe	
		Peripheral zone		Central zone					
		long diameter μ	short diameter μ	long diameter μ	short diameter μ	long diameter μ	short diameter μ	long diameter μ	short diameter μ
Immediately after birth	male	243* (452—139)**	174 (313—104)	139 (208—104)	104 (139—87)	139 (208—104)	139 (156—69)	139 (313—87)	104 (208—69)
40 days	female	191 (313—139)	139 (226—87)	156 (295—121)	104 (156—69)	156 (261—121)	104 (208—69)	69 (139—34)	52 (104—34)
4 months and a half	female	295 (696—191)	226 (574—139)	191 (243—139)	156 (191—121)	156 (243—104)	121 (174—87)	156 (261—104)	121 (226—104)
6 years	male	452 (800—331)	331 (557—191)	261 (365—191)	191 (261—139)	226 (278—191)	174 (261—139)	295 (522—191)	208 (435—121)
15 years	male	522 (1078—348)	400 (991—261)	330 (730—226)	226 (417—156)	330 (556—261)	226 (295—156)	243 (400—226)	174 (226—104)
18 years	female	487 (591—139)	313 (452—191)	365 (870—261)	243 (556—174)	365 (574—261)	261 (469—174)	278 (400—226)	208 (348—121)
28 years	male	376 (696—261)	273 (522—174)	331 (522—243)	226 (382—174)	295 (487—191)	174 (313—104)	208 (348—156)	139 (191—121)
31 years	male	435 (643—313)	261 (365—174)	330 (435—261)	226 (330—174)	295 (574—174)	156 (243—121)	226 (330—174)	121 (174—87)
33 years	male	504 (678—400)	348 (556—208)	487 (783—348)	330 (504—226)	365 (609—295)	243 (348—191)	330 (609—191)	208 (384—104)
37 years	male	400 (609—295)	261 (417—174)	382 (574—278)	295 (469—174)	313 (435—261)	208 (365—139)	278 (469—156)	174 (261—104)
42 years	male	313 (417—295)	243 (365—208)	348 (452—278)	261 (400—208)	295 (435—278)	243 (348—174)	261 (348—191)	191 (313—121)
43 years	male	417 (783—330)	278 (382—208)	382 (556—295)	261 (382—208)	382 (556—295)	226 (313—156)	313 (400—243)	226 (313—174)
43 years	male	626 (1096—435)	365 (748—208)	591 (957—452)	452 (609—295)	469 (678—313)	330 (556—208)	295 (452—208)	208 (295—139)
45 years	male	455 (556—382)	348 (539—226)	365 (469—295)	295 (452—174)	422 (469—261)	208 (322—139)	261 (400—191)	208 (313—156)
46 years	male	295 (556—243)	191 (295—139)	330 (522—243)	191 (261—174)	275 (452—208)	208 (313—174)	226 (365—174)	156 (243—104)

47 years	male	447 (678—348)	278 (400—191)	447 (678—330)	295 (452—191)	382 (626—313)	226 (348—139)	261 (400—121)	139 (261—87)
47 years	male	417 (696—313)	261 (382—156)	382 (765—278)	243 (348—191)	295 (522—208)	174 (295—139)	278 (417—208)	156 (261—121)
57 years	male	504 (852—348)	313 (435—208)	452 (574—365)	313 (452—226)	452 (556—365)	295 (452—243)	243 (348—208)	191 (313—139)
61 years	female	243 (313—174)	156 (278—87)	226 (435—174)	156 (278—121)	261 (435—191)	139 (261—69)	226 (348—171)	156 (226—121)
68 years	male	295 (487—226)	208 (330—121)	295 (400—261)	243 (348—174)	348 (678—243)	174 (313—87)	226 (313—174)	174 (295—139)

* Averaged value of diameters. ** Range.

cells found in newborn babies may be due to hormonal stimulation in connection with the preparations for child birth by the mother.

Müller (1896), Sumita (1911), Vogel (1914) and Murray (1927) explained the same event to be caused by the postmortal change. Wegelin (1926) proved also it to be due not only in the newborn glands but also in the adult glands to the postmortal autolytic process. Gloor (1926) also stated that desquamation of the follicle cells found in the newborn glands depends in intensity upon the length of time elapsing from death to fixation. Karpowa (1931) described that the desquamation and colloid disappearance are not a phenomenon typical of the newborn gland. Ewers (1936) suggested that the postmortal desquamation is increased in the young but decreased in the old.

The usual desquamation and loosening of the follicle cells observed not only at or shortly after birth but also in later periods in the present investigation may confirm the views of Karpowa (1931) and Gloor (1926).

The follicle cells of the human thyroid gland have been described to vary from flat cubical to columnar form (Sobotta, 1915). Rice (1931) reported that the follicle cells vary in height with age: The follicle cells at birth are cubical and columnar in type, and remain in almost the same condition in infancy. Between 17 and 25 years they become partly flat in type which does not exceed the cubical type in proportion, and thereafter become predominantly cubical. v. Ebner (1902) described that the follicle cells of the adolescent glands are columnar. Isenschmid (1910) wrote that the follicle cells decrease as a rule in their height during childhood although variable extremely from individual to individual. Sanderson-Damberg (1911) stated that the follicle cells in the 15 to 25 year olds are cubical. Further, Wegelin (1926) found that the follicle cells are predominantly cubical in adults but flat or endothelial in follicles containing abundant colloid. An examination of the senile gland (Clerc, 1912) elucidated that the follicle cells are usually divisible into three forms — the first usually cubical in type, the second columnar with darkly stained oval nuclei in the Sanderson-Damberg's bolster-like swellings, and the third a type different from the former two, large in size and with light cytoplasm and large nucleus. ASCHOFF (1938) pointed out that the follicle cells are low in advanced age. On the other hand, ORATOR and SCHLEUSSING (1931) found in the senile gland that the follicle cells increase in height in contrast with the size decrease of the follicles and are rarely squamous but rather often cubical to low columnar. A report of the newborn gland (HESSELBERG, 1910) described that the follicle cells are cubical in most of the follicles, squamous in the large follicles and high columnar in the tubes (Schläuche).

Quantitative measurements of the follicle cells also have been reported: VERSON (1872): 10 to 16 μ in height; v. EBNER (1902): average 9 to 13 μ and WEGELIN (1926): 8 to 9 μ and the values described here are approximately similar to the present data. In general agreement with the data of RICE (1931), the present results showed that the follicle cells are cubical until puberty (Fig. 21) but become variable — squamous to low cubical — shortly after puberty, remain almost the same in adult life but unexpectedly often high cubical in the presenium and senium (Fig. 22). DOGLIOTTI *et al.* (1933, 1935) found the size increase of the follicle cells in the senium to be a phenomenon of compensation for the senile decline of metabolism. Recently, in coincidence with these histological results, SCAZZIGA *et al.* (1955) pointed out that thyroxinaemia and hyperfunction of the thyroid gland occur without increase of the basal metabolic rate in the senium, and this hyperthyroidism compensates for the involution.

Classification of the follicle cells into principal and colloid cells and also fusion cells (ALLARA, 1938) could not be confirmed in the present study. According to ALLARA (1937, 1938), the colloid cells and fusion cells mean different functional phases of the follicle cells and occur often in the gland with signs of hyperfunction, where fusion appears with the object of discharging rapidly and suddenly large amounts of hormone into the circulation.

Yellowish brown pigment granules found in the follicle cells begin to appear already in the 6 year old and increase significantly in amount in the presenium and abundant in the senium (Fig. 22). WEGELIN (1926), and BERBERICH and FISCHER-WASELS (1932) considered them to be waste pigment granules. v. GIERKE (1923) described that the waste pigment granules appear in the follicle cells from the forties on. CLERC (1912) found them in those over 50 years. According to HÄBERLI (1916), the waste pigment granules in the follicle cells appear sometimes in the 30 years old and increase from 50 years on.

The follicle cells in the Sanderson-Damberg's bolster-like swellings of the follicle walls observed in the present study are identical in appearance with those reported (SANDERSON-DAMBERG, 1911; ORATOR and SCHLEUSSING, 1931; HELLWIG, 1933) (Fig. 31) and show no mitotic figures. Further, the present study showed that the mitotic figures are not found also in those of other ordinary parts of the follicles throughout postnatal life. STEIN (1938) reported also that no cell division is observed in follicles examined in normal adult thyroid glands.

Giant nuclei of the follicle cells are found not only in small follicles but also in medium-sized to large follicles. ISENSCHMID (1910) found them in children's glands while SANDERSON-DAMBERG (1911) observed them in adolescent glands. The present study showed that they appear often in late adult life, the presenium and senium.

The interfollicular epithelium (interfollicular epithelial cells) of the human thyroid gland has been summarized to be abundant in childhood, lesser in adult life and absent in the senium (SOBOTTA, 1915) and has received so far different names (solid cell masses, cell nests, interstitial cells, macrothyrocytes and parafollicular cells). GOORMAGHTIGH *et al.* (1934) described that the interstitial cells do not appear in the infant and adult glands but rather become apparent in senile involution of the gland. COOPER (1925) described that the solid cell masses become larger and more numerous as the months advance in infancy, the cells among the masses forming vesicles around the colloid droplets, and finally become insignificant in old age. v. EBNER (1902) found earlier the solid cell cords and nests in many of the lobules of the adult gland. ALLARA (1951 b) found the parafollicular cells in newborn babies by the use of Feulgen's reaction. BONFIGLI *et al.* (1960) observed that the interfollicular epithelium is increased until 4 years, decreased gradually from 4 to 20 years, is almost completely absent between 20 and 50 years and disappears at over 50 years.

The differentiation of the interfollicular epithelium has been discussed differently — 1. from the follicle epithelium (ALLARA, 1939), 2. from the budding process of the follicle wall (ALTMANN, 1940), 3. from empty compressed follicles (ISENSCHMID, 1910), 4. from disintegration of the follicles (ZECHEL, 1933) and 5. from the rest of the embryonic cell masses (WÖLFLER, 1880; ZECHEL, 1933). The functional significance of the interfollicular epithelium has been often reported in man to form the follicles (MÜLLER, 1896; LOBENHOFFER, 1909; KRAUS, 1914; HUECK, 1922). BONFIGLI *et al.* (1960) observed that the increased amount of interfollicular epithelium corresponds in time relation to the more elevated values of basal metabolism. According to ALLARA (1939), the interfollicular epithelium varies in number and appearance depending upon different phases of function and develops from the follicle epithelium and inversely to the follicles. STEINER (1948) found the parafollicular cells in normal and goitrous glands and stated that they have the function of regulating hormone production and transportation.

BARGMANN (1939) suggested in v. Möllendorff's Handbuch that the interfollicular cells do not appear so regularly in the human thyroid gland as in small mammals. RIENHOFF (1929) suggested by making wax plate reconstruction models that the small cell nests are nothing but tangential sections of follicles. THOMAS (1934) suggested that the satellite follicles in the human thyroid gland are homologous with the interstitial cells found in small mammals.

The detailed examination of the literature and especially the pictures included showed that the interfollicular cells reported in the human thyroid gland, except for those reported by SANDRITTER *et al.* (1954), may be in sharp contrast in appearance with those observed in small mammals. The present observations showed that a small number of the parafollicular cells in the glands of two months old female child and 55 years old woman (Figs. 21 and 22) are completely identical with those reported by Nonidez (1932), the present author and his colleagues. The parafollicular cells have a large oval or polygonal cell body and a large, slightly eosinophilic round to oval nucleus with a loose chromatin reticulum and a large prominent nucleolus, and show the same histological positions in, on and between the follicles. Although the present study could not clearly elucidate their differentiation from the follicle cells or other sources, the observation of the parafollicular cells found just near a cyst which was completely different from ordinary follicles and of ultimobranchial origin may support the possibility of their ultimobranchial origin (see Addendum).

The residual tissues of branchiogeneous origin — remnants of the ultimobranchial body and thymus IV, together with the thyroglossal duct — have been described as being contained in the human thyroid gland (see WEGELIN, 1926 and; BARGMANN, 1939). ERDHEIM (1904) found branchiogeneous cysts in a side concerned with partial aplasia of the thyroid gland. GETZOWA (1907) observed also structures of ultimobranchial origin — main and accessory cysts together with cell conglomerates — in the atrophic thyroid gland of cretins and idiots. KLOEPPEL (1910) found two structures — 1. small nests of squamous epithelium and 2. cell conglomerates which look like lymphatic and thymic tissues in newborn and senile glands. WEGELIN (1926) described the cysts of ultimobranchial origin in a case of aplasia of the thyroid gland in a newborn baby. WATZKA (1933) wrote that the ultimobranchial body usually disappears enclosed by growing thyroid lobes but appears in cases of thyroid aplasia and hypoplasia with its structure outside the thyroid gland.

The present study showed that the residual structures of ultimobranchial origin remain sometimes singly or as a part of the parathyro(IV)-thymo(IV)-ultimobranchial complex during normal development of the human thyroid gland (Table 7 and Figs. 23 to 26). The residual structures consist of solid cell cords and cell conglomerates, sometimes together with cysts of different sizes and are found not only in the posterior part of the peripheral zone of the lobe but also in the central zone. The finding has been also confirmed in the prenatal development of the human thyroid gland (SUGIYAMA et al., 1959a). The cell cords and cell conglomerates found in the present study are completely identical with those of the complex found in the prenatal development. These solid cell cords and cell conglomerates remain to be seen whether they are converted directly to the parafollicular cells or not (see Addendum).

ZIELINSKA (1894) and KLOEPPEL (1910) found no colloid in the majority of newborn thyroid glands but its sparse distribution in the minority. The difference of colloid distribution between the goiter-free and goitrous districts has been also reported in the newborn gland (SCHMELLING, 1934). The present study showed that the colloid is contained uniformly in all of the follicles immediately after birth (Fig. 6). ISENSCHMID (1910) wrote that the colloid of the children's gland is usually dilute. SOBOTTA (1915) described that the colloid is dilute in the young and dense, strongly acidophilic and homogeneous, with marginal, central and eccentrical vacuoles in the adult. COOPER (1925) described that the colloid becomes hard and brittle in late adult life, but absent in many follicles or dilute and feebly stained in old age. CLERC (1912) found that the colloid increases in consistence in old age and decreases marginal vacuolation. DOGLIOTTI *et al.* (1933, 1935) found diminution of the colloid as a result of increased function in the senile gland. The present results showed that the colloid appears to change in amount in parallel with the change of the follicular pattern with age and is maximum in amount from the end of early adult life to the beginning of late adult life. The colloid observed in the present study, throughout postnatal life, shows not always a constant relation in staining, concentration and vacuolation with the follicle condition (size, shape and location) and follicle cell condition (height and form). However, it may be said that the colloid contained in very small and small follicles shows feeble staining while the colloid contained in medium-sized and large follicles shows moderate staining with some variability. The age dependence of the colloid staining is as follows: It is relatively poorly stained at birth and remains moderately eosinophilic towards the beginning of late adult life, thereafter becomes variable in staining towards the presenium and feeble in the senium.

The usual desquamated cells found not only at or shortly after birth but also in other later periods appear to be due to cadavernous change which varies in intensity depending upon the length of time elapsing between death and fixation. Desquamated cells together with wandering cells found in the colloid before and in the presenium and senium may be explained to be a vital phenomenon related with involution of the follicles and follicle cells (Fig. 33). Similarly, EWERS (1936) described that intravitam desquamation occurs chiefly in old people and is related to a physiological process. HELLWIG (1951) found macrophages in the colloid of the human gland, which later migrate again to the circulation after taking the colloid.

The arteries and veins show no histological characteristics specific to the human thyroid gland, but the arteries, medium-sized and small, show two kinds of formation, semispherical arterial buds (HORNE, 1892; SCHMIDT, 1894; GETZOWA, 1905; ISENSCHMID, 1910; SANDERSON-DAMBERG, 1911; PETERSEN, 1935; KUX, 1935) and funnel-shaped sphincter apparatuses (KUX, 1935). Gilpin (1934) expressed that the arterial buds are nothing but a pressed part of the vascular wall.

The present data showed that the arterial buds appear far more often than the sphincter apparatuses (Fig. 27 to 29). The funnel-shaped sphincters appear exclusively just at the branching point as two lip-like valvules in longitudinal section, while the arterial buds are found as semispherules not only at the branching points and their neighborhood but also in the ordinary parts of the arteries and further in the arteriovenous anastomoses. According to MAJOR (1909), the arteries which pass between the lobules are 0.03 mm and those supplying each follicle — follicular arteries are 0.0125 mm. JOHNSON (1955) pointed out the presence of the lobular arteries supplying each lobule which in turn provide capillary beds to surround the follicles. The arteries related to the arterial buds and sphincter apparatuses observed (the parent arteries — 60 to 30 μ in diameter and their branches — 50 to 30 μ) may range in order from arteries larger than the interlobular arteries (MAJOR, 1909) to arteries larger than the follicular arteries. The present observations, further, suggested that the two kinds of artery formation have a similar situation in histology and topography and take an important role in regulating the blood flow related to thyroid hormone production. However, it is interesting to find that more frequent occurrence, in the posterior half of the lobe and between 30 to 60 years, of the arteries concerned with arterial buds appears to be coincident in topographic and time relation with the regression of large follicles in this zone of the lobe. It may be supposed that the arterial buds play rather a role of adjusting negative thyroid function and induce the histological regression to be found here.

Perifollicular capillaries, which are abundant and often engorged from birth to the beginning stage of late adult life, appear to have an intimate relation with the progressive functional phase of the gland. The subsequent decrease of the capillaries which is marked in the senium and in the peripheral zone of the lobe, may be related to regression of the gland. This agrees with the data of McGAVACK *et al.* (1959) who found a decreased blood supply, a gradual decrease in basal metabolic rate and thyroid uptake of radioiodine I^{131} after 50 years.

ALLARA (1933) and WETZEL (1938) described in newborn babies that the capsule is divisible into two layers. The present data also showed that the capsule of adults is divisible into two layers, internal and external, in the major part, with the internal layer consisting of thin dense connective tissue with elastic fibers, and the external layer of broad loose connective tissue with abundant fat tissue in which steatoblast tissue appears in early childhood, and indivisible, in the minor part, where it is transformed directly into the perimysium of the infrahyal muscles and the adventitia of the trachea and esophagus. ALLARA (1933) reported that elastic fibers are absent here in the suckling period. This is confirmed also in the present data. Further, the present data showed that the two layers contain no argyrophilic fibers and are maintained in almost the same state of arrangement from the newborn period to the senium (Figs. 6 to 20).

The primary and secondary septums with elastic fibers but without argyrophilic fibers are pushed into the interior of the gland, containing blood vessels and nervous bundles, sometimes together with small islets of fat tissue. The secondary septums may correspond to the interlobular connective tissue or septums (Figs. 9, 13, 18 and 20). The septums, primary and secondary, appeared to be formed here and there already in the newborn gland. The secondary septums later become indistinct with growth of the follicles, especially from early adult life on, but are relatively well demonstrable by detecting the presence of increased elastic fibers.

Perifollicular connective tissue consists of dense networks of argyrophilic fibers with a few elastic fibers and is increased in width in the presenium and senium, especially near the septums and capsule. The elastic fibers appear merely as continuations of those in the adventitia of the blood vessels from 7 years on and increase in the presenium and senium.

WEGELIN (1910, 1926) described that the stroma of the gland is significantly more finely formed in newborn babies than in adult life and connective tissue fibers increase in the intralobular stroma in the senium. BUCCIOLINI (1954) wrote that the stroma of the senile gland does not always constantly show fibrotic alteration. KASHIWAMURA (1901) found more abundantly interlobular tissues in childhood than in adult life and again so in the senium. ALLARA (1934) described that the increase of connective tissue is not found in old age but rather an increase of elastic fibers occurs. DOGLIOTTI *et al.* (1933) described that the connective tissue containing elastic fibers remains generally unchanged or slightly increased from over 55 to 60 years. v. GIERKE (1923) described in ASCHOFF's textbook that the connective tissue is increased in the senium, especially markedly in the glands from goitrous districts. OOSUGI (1960) found a gradual but slight increase of fibrosis with age in the glands. According to TAKAYA *et al.* (1962), the elastic fibers found in the lobules increase from 20 years and tend to atrophy after 60 years.

Lymphatic tissue does not appear in children but often from 30 years, especially in women and decrease in the senium (HECKER, 1922). LAMPAR (1946) reported that lymphatic foci do not occur in infancy but rarely in adolescence, and increase to 4% of cases examined in men and to 17% in women, between 31 to 88 years. On the other hand, LEWIS (1938) reported that the lymphocyte crowds appear in 23% of cases of 5 to 8 decades and in 40% of cases of 5 to 10 years and show no special relation with diseases. WEGELIN (1926) stated that the lymphatic herds cannot be found in newborn babies and young children. Further, SIMMOND (1913) described that the lymphatic herds are found often in apparently normal glands, especially in those of women, but very rarely before puberty.

The present data showed that lymphocyte infiltrations occur very rarely among follicles or around small blood vessels near the capsule, and are small in degree without developing to nodules.

Summary

Histological studies of 326 human thyroid glands ranging in age from immediately after birth to 88 years were made from the viewpoint of postnatal development.

1. Immediately after birth the thyroid gland is not solid, but consists of all colloid-containing follicles. The thyroid gland gradually develops, attains full maturity and slowly involutes, passing through several stages of different follicular type, microfollicular in the newborn and suckling periods and in early childhood (one year to 5 years), microfollicular and microfollicular-macrofollicular in late childhood (6 to 12 years) and microfollicular-macrofollicular in puberty (13 to 15 years), microfollicular-macrofollicular and macrofollicular in the first half (16 to 19 years) of early adult life and macrofollicular in the second (20 to 24 years), still further macrofollicular during the beginning (25 to 29 years) of late adult life, macrofollicular or transitive macrofollicular and macrofollicular-microfollicular during the middle (30 to 39 years), transitive macrofollicular and macrofollicular-microfollicular during the end (40 to 44 years), further macrofollicular-microfollicular in the presenium (45 to 49 years) and finally microfollicular in the senium.

2. Follicles range in diameter from 20 to 800 μ, rarely over 1000 μ in adults. Large follicles are usually about 400 to 600 μ in the average long diameter. Large follicles show highest values in diameters in the peripheral zone of the lobe, especially in its posterior part, and lower values in the central zone, especially in its anterior half, and least values in the isthmus and still more smaller values in the pyramidal lobe.

3. The large follicles, singly and usually in groups, together with their surrounding smaller follicles, form thyromeres which are similar in arrangement to the collecting duct system (or the central canal system) and correspond to the lobules in histogenetical sense. The thyromeres appear more frequently in the posterior part of the peripheral zone of the lobe and in the posterior half of the central zone and are greater in scale than in other parts.

4. Until the beginning of late adult life this difference is well maintained but thereafter gradually disappears—— large follicles and thyromeres placed in the posterior half of the lobe become respectively in diameter and scale close to those

situated in the anterior half of the lobe, in the isthmus, and further in the pyramidal lobe. The histological differentiation appears to increase in degree through the pyramidal lobe, the isthmus and the anterior half of the lobe towards the posterior half of the lobe, while the histological regression appears to be exaggerated in the above final zone.

5. Follicles associate with each other at birth and are embryonic in type. They maintain this situation until 2 years and thereafter dissociate from each other.

6. SANDERSON-DAMBERG's bolster-like swellings and their relatives occur at considerably high rates, and increase earlier in women — in early adult life and later in men — in the presenium.

7. Follicle cells are high cubical until puberty, but remain variable, squamous to low cubical during early and late adult life, and are unexpectedly often high cubical in the presenium and senium. Yellowish brown pigment granules appear in the apical zone and lateral to the nuclei from 6 years on and in abundance in the presenium and senium.

8. Parafollicular cells which are completely identical in histology with those reported in other mammals appear rarely and are situated in, on and between the follicle walls, singly and in groups. The nuclei are larger than those of the follicle cells and slightly eosinophilic as a whole and contain a loose chromatin reticulum and a prominent nucleolus. The cell body is also larger than that of the follicle cells.

9. In the posterior half of the lobe, structures of ultimobranchial origin appear sometimes and consist of solid cell cords and conglomerates, and further a few to several cysts. They remain longer in the senium — eighties.

10. The colloid appears to change in amount with age in parallel with the change of the follicular pattern and is maximum from the end of early adult life to the beginning of late adult life. The colloid is relatively feebly stained at birth and becomes moderately eosinophilic towards the beginning of late adult life, thereafter remains variable in staining and feeble in the senium. Most of the desquamation of follicle cells into the colloid are caused by cadavernous change, but the occasional occurrence of desquamated follicle cells with wandering cells before and in the presenium and senium can be explained as a sign of intravitam degenerative change which occurs physiologically in these periods.

11. The funnel-shaped sphincter apparatuses appear sometimes in early life and are found just at the branching point of the arteries, while the arterial buds occur often from over 30 to 60 years and are found singly or in groups not only at or near the branching points of the arteries but also in the ordinary non-branching parts of the arteries and further in the arteriovenous anastomoses.

12. The capsule is divided in the major part into two layers, internal and external. The internal layer consists of dense connective tissue with elastic fibers but without argyrophilic fibers and the external layer of loose connective tissue with abundant fat tissue but without argyrophilic fibers. The septums, primary and secondary, are dense connective tissues with abundant elastic fibers but without argyrophilic fibers. The secondary septums correspond to the so-called interlobular connective tissue but have no relation in arrangement with the thyromeres. Perifollicular connective tissue consists of dense networks of argyro-

philic fibers, and contains sometimes elastic fibers in a small amount in adult life and slightly abundantly in the presenium and senium. During early life, the elastic fibers are not found here.

Acknowledgements. The author wishes to express his sincere gratitude to Prof. Dr. MASAZUMI MIYAKAWA, the Department of Pathology and to Prof. Dr. KANJI FURUTA, the Department of Forensic Medicine, for their kindness in supplying a considerable part of the materials used, and further to Dr. SADAOMI FURUI for his kind help in recording accurately the clinical and pathological data of the entire material. The author wishes to thank cordially Mr. RIHEI TABATA for his technical assistance throughout the whole period of this study in the Department of Anatomy.

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Although a great deal has been published on the histology of the thyroid gland, the literature presented here is chiefly limited to that of the human thyroid gland.

Addendum

The present author and his research colleagues have studied the origin of the parafollicular cells by electron microscopy and elucidated that the parafollicular cells are of ultimobranchial origin.

ISHIKAWA (1965) found in rat embryos that the direct contact (fusion) of the ultimobranchial body with primitive thyroid follicle tissue in earlier stages (18 mm CRL, 17 days) persists as such — in a parafollicular position — towards term and leads some of its epithelial cells to form the young forms of the parafollicular cells. SATO et al. (1966) found also in adult mice that the parafollicular cells develop from the ultimobranchial cyst. Further, the present author and his colleagues found the homology of the parafollicular cells in the epithelial cells of the ultimobranchial body of lower vertebrates by electron microscopy. This will be published soon.

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